Briefing Document

Anti-Infective Drugs Advisory Committee Meeting

Telavancin for the Treatment of Nosocomial Pneumonia

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LIST OF ABBREVIATIONS

ACE	angiotensin converting enzyme
AE	adverse event
AIDAC	Anti-infective Drugs Advisory Committee
ALI	acute lung injury
ALT	alanine aminotransferase
AM	alveolar macrophages
APACHE	Acute Physiology and Chronic Health Evaluation
APD	action potential duration
ARF	acute renal failure
AT	all-treated (analysis population)
AT-ATS/IDSA	American Thoracic Society/Infectious Disease Society of America all-treated (analysis population)
ATCC	American Type Culture Collection
ATS	American Thoracic Society
AUC	area under the concentration-time curve
BAL	bronchoalveolar lavage
BBS	blind bronchial suctioning
BMI	body mass index
BUN	blood urea nitrogen
CE	clinically evaluable (analysis population)
CFU	colony forming unit
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CPIS	Clinical Pulmonary Infection Score
CPMP	Committee for Proprietary Medicinal Products
CPR	cardiopulmonary resuscitation
CrCL	creatinine clearance
cSSSI	complicated skin and skin structure infections
CT	computed tomography
EC	Ethics Committee
ECG	electrocardiogram
ELF	epithelial lining fluid
EMA	European Medicines Agency
EOT	end of therapy
ETA	endotracheal aspirate
FDA	Food and Drug Administration
GLP	Good Laboratory Practices
HABP	hospital-acquired bacterial pneumonia
HAP	hospital-acquired pneumonia
HCAP	health care-associated pneumonia

LIST OF ABBREVIATIONS

HCP	Healthcare Provider
hERG	human ether-a-go-go-related gene
HIV	human immunodeficiency virus
hVISA	heterogeneous vancomycin-intermediate *S. aureus*
IBW	ideal body weight
IC_{50}	50% inhibitory concentration
ICU	intensive care unit
IDSA	Infectious Disease Society of America
IM	intramuscular
IRB	Institutional Review Board
IV	intravenous
LZD	linezolid
MAT	modified all-treated (analysis population)
MBC	minimum bactericidal concentration
MDR	multidrug-resistant
ME	microbiologically evaluable (analysis population)
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
MOF	multiorgan failure
MPP	modified per protocol (analysis population)
MRSA	methicillin-resistant *S. aureus*
MSSA	methicillin-sensitive *S. aureus*
NDA	New Drug Application
NNIS	National Nosocomial Infections Surveillance
NP	nosocomial pneumonia
NSAID	nonsteroidal anti-inflammatory drug
NVAHAP	non–ventilator-associated hospital-acquired pneumonia
NVANP	non–ventilator-associated nosocomial pneumonia
OAP	Office of Antimicrobial Products
OND	Office of New Drugs
$PaCO_2$	arterial partial pressure of carbon dioxide
PAP	population analysis profiling
PCS	potentially clinically serious
PD	pharmacodynamic
PEA	potentially effective concomitant antibiotics (other than those being clinically evaluated)
PK	pharmacokinetic
PO	oral
PP	per protocol
PSB	protected specimen brush

LIST OF ABBREVIATIONS

QTc	corrected QT interval
QTcB	corrected QT interval using Bazett's correction
QTcF	corrected QT interval using Fridericia's correction
R	resistant
REMS	Risk Evaluation and Mitigation Strategy
S	susceptible
SAE	serious adverse event
SAP	statistical analysis plan
SEC	squamous epithelial cells
SIRS	Systemic Inflammatory Response Syndrome
SOC	system organ class
TOC	test of cure
TLV	telavancin
US	United States
VABP	ventilator-associated bacterial pneumonia
VAN	vancomycin
VAP	ventilator-associated pneumonia
VISA	vancomycin-intermediate *S. aureus*
WBC	white blood cell

1 EXECUTIVE SUMMARY

Telavancin (VIBATIV®) was approved for the treatment of complicated skin and skin structure infections (cSSSIs) in the United States (US) in September, 2009 and in Canada in October, 2009. Additionally, telavancin was approved for nosocomial pneumonia (NP) (also referred to as hospital-acquired pneumonia [HAP]), including ventilator-associated pneumonia (VAP) in the European Union, Norway, and Iceland in September, 2011, based on two international studies of NP comprising a total of 1503 subjects. An estimated 125,000 patients have been treated with telavancin since September 2009.

Despite advances in antimicrobial therapy, NP, including VAP, remains an important cause of morbidity and mortality (2). There is a critical need for new therapies, particularly therapies with limited potential for resistance, and the prospect for new agents in this indication in the near future is extremely limited.

This document provides the rationale for approval of telavancin in the US for the treatment of NP.

1.1 Telavancin for Nosocomial Pneumonia

The proposed indication for telavancin is for the treatment of patients with NP (also referred to as HAP), including VAP, caused by susceptible isolates of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-resistant isolates) and *Streptococcus pneumoniae*.

Telavancin is a lipoglycopeptide that has potent bactericidal activity against Gram-positive bacteria including clinically relevant Gram-positive pathogens: staphylococci (including methicillin-resistant and vancomycin-intermediate strains), streptococci (including multidrug-resistant pneumococci), enterococci (including many vancomycin-resistant strains), Gram-positive anaerobes such as clostridia (including *C. difficile*), and other less commonly encountered pathogens. The bactericidal activity of telavancin results from a dual mode of action that includes inhibition of cell wall synthesis and disruption of bacterial plasma membrane function. Results from in vitro studies indicate that telavancin has a low potential to select for resistance. Importantly, development of resistance to telavancin in clinical studies has not been observed. Although some vancomycin-resistant enterococci (vanA genotype) have reduced susceptibility to telavancin, there is no known cross-resistance between telavancin and other classes of antibiotics. Organisms resistant to daptomycin or linezolid remain susceptible to telavancin at the proposed minimum inhibitory concentration (MIC) breakpoints. In vivo pharmacology studies showed that telavancin is efficacious and demonstrates bactericidal activity in models of soft tissue (neutropenic murine thigh, murine subcutaneous infection), deep seated (rat and rabbit endocarditis), systemic (murine bacteremia) and lung (murine pneumonia) infections.

1.2 Development and Regulatory History

1.2.1 Development and Regulatory Milestones in Nosocomial Pneumonia

The design for the two Phase 3 studies (Study 0015 and Study 0019) was based on the July 1998 Food and Drug Administration (FDA) Guidance for Industry: "Nosocomial Pneumonia – Developing Antimicrobial Drugs for Treatment" and "Developing Antimicrobial Drugs – General Considerations for Clinical Trials" and in accordance with the European Medicines Agency (EMA)/Committee for Proprietary Medicinal Products (CPMP) guidance document: "Note for Guidance on Evaluation of Medicinal Products Indicated for Bacterial Infections" CPMP/EWP/558/95 Rev 1, 22 April 2004.

The studies were conducted between early 2005 and mid-2007, after discussion with the FDA regarding the Phase 3 clinical development program for telavancin for NP at an End of Phase 2 meeting in July 2004. The statistical analysis plan (SAP) was finalized and submitted to the FDA before blinded treatment assignments were known, and the SAP was subsequently discussed with the FDA at the pre-New Drug Application (NDA) meeting in March 2008. In January 2009, the NDA was submitted.

After submission of the NDA, the Division noted that assessment of the noninferiority of telavancin would depend on the analysis of the all-cause mortality data. In response to the increasing interest in all-cause mortality as an outcome measure for NP, Theravance made the decision to return to the clinical sites and collect vital status data through Study Day 49 for each study participant.

1.2.2 Development Program in Nosocomial Pneumonia

The Phase 3 NP program included two studies, Studies 0015 and 0019, which were randomized, double-blind, active-controlled, parallel-group, multicenter, multinational trials of identical design. The objective of each study was to demonstrate noninferiority of telavancin to vancomycin in the treatment of NP due to Gram-positive pathogens, with a focus on infection due to methicillin-resistant *S. aureus* (MRSA).

The study entry criteria were selected to enroll patients who had clinical and radiographic evidence of NP. Patients at risk for poor outcomes, such as the elderly, patients with bacteremia, or those with comorbid conditions, such as moderate or severe renal impairment were not excluded from the study population. The studies were designed to compare the efficacy of two drugs with activity against Gram-positive pathogens; therefore, the use of concomitant Gram-negative therapy allowed per protocol (aztreonam or piperacillin/tazobactam) was left to the investigator's discretion.

The dosage of telavancin used in the studies was 10 mg/kg intravenous (IV) q 24 hours in patients with normal renal function (creatinine clearance [CrCL] > 80 mL/min) and mild renal impairment (CrCL 50−80 mL/min) and was to be adjusted in patients with moderate (CrCL 30−50 mL/min) or severe (CrCL < 30 mL/min) renal insufficiency. Vancomycin 1 g IV q 12 hours was the comparator used in these studies. The vancomycin regimen was to be monitored and dosage adjusted according to the institutional policy at each

investigative site, by unblinded personnel not involved in assessment of patient outcome or care.

The prespecified primary efficacy analysis was an evaluation of telavancin's noninferiority to vancomycin, with respect to clinical response at the test of cure (TOC) assessment, employing a prospectively determined noninferiority margin (the Δ) of 20%, meaning that noninferiority would be declared if the lower bound of the 95% confidence interval (CI) for the difference in cure rates (telavancin – vancomycin) exceeded $-\Delta$. The margin was consistent with other contemporary registrational trials in the same indication.

Death events were collected during the conduct of Studies 0015 and 0019 as a secondary efficacy endpoint and as a safety outcome. The studies were not designed to evaluate mortality at a specified time point and all-cause mortality was not a prespecified endpoint. The studies did not control for factors that may have resulted in unrelated, inevitable death, such as decisions to limit medical care (eg, "Do Not Resuscitate," or "Comfort Care Only"), baseline differences in acuity of illness, or the presence of comorbidities.

Combined, the studies enrolled a total of 1503 adult NP patients, 427 of whom had VAP.

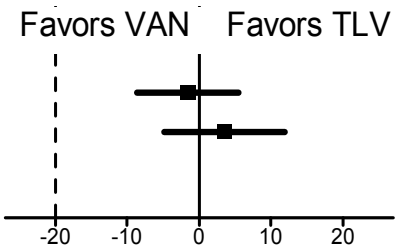
1.2.3 Summary of Primary Efficacy Endpoint, Clinical Response

The studies demonstrated that telavancin 10 mg/kg administered intravenously every 24 hours for 7 to 21 days was noninferior to vancomycin in treating patients with NP caused by susceptible strains of Gram-positive pathogens (Figure 1). Analysis of the primary efficacy endpoint, clinical response at the TOC, in the coprimary all-treated (AT) and in the clinically evaluable (CE) analysis populations consistently showed that telavancin was noninferior to vancomycin in patients with NP. The lower bound of the 95% CI of the treatment difference between telavancin and vancomycin in both coprimary analysis populations in each study was greater than −10%.

Figure 1: Clinical Cure Rates at TOC – AT and CE Populations, Studies 0015 and 0019

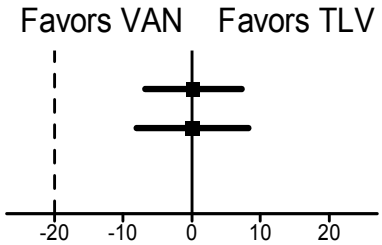
Study 0015

	N	TLV %	VAN %	Delta	95% CI[a]
AT	746	57.5	59.1	-1.6	[-8.6, 5.5]
CE	313	83.7	80.2	3.5	[-5.1, 12]



Study 0019

	N	TLV %	VAN %	Delta	95% CI[a]
AT	757	60.2	60.0	0.2	[-6.8, 7.2]
CE	341	81.3	81.2	0.1	[-8.2, 8.4]



[a] Difference in cure rates (telavancin – vancomycin); 2-sided 95% CI on the difference. Aggregate analysis was stratified by study.
AT = all-treated; CE = clinically evaluable; TLV = telavancin; VAN = vancomycin; TOC = test of cure; CI = confidence interval.

A prespecified objective of the NP program was to analyze the aggregated data from Studies 0015 and 0019 to test whether telavancin 10 mg/kg was superior to vancomycin in the treatment of NP due to MRSA. In the analysis that included all MRSA-infected patients (including those with mixed infections), telavancin did not demonstrate superiority over vancomycin. However, in patients with only *S. aureus*, the group treated with telavancin had a significantly higher cure rate compared with the group treated with vancomycin. The clinical response rates for telavancin in patients with only MRSA or methicillin-sensitive *S. aureus* (MSSA) were consistently numerically higher (by 7.9% and 12.2%, respectively) than those for vancomycin. Additionally, for single pathogen infections in the microbiologically evaluable (ME) population due to *S. aureus*, including MRSA and MSSA, with vancomycin MIC ≥ 1.0 µg/mL (Table 1), cure rates were significantly higher in the telavancin group (~87%) compared with the vancomycin group (~74%). Finally, among a small cohort of patients found to have heterogeneous vancomycin-intermediate *S. aureus (*hVISA) pneumonia (without mixed infection), the cure rates for telavancin were numerically higher (71%) compared with vancomycin (38%).

Table 1: Clinical Response at TOC According to In Vitro Susceptibility to Vancomycin of S. aureus Recovered at Baseline – ME Population, Studies 0015 and 0019

	VAN MIC (µg/mL) ≤ 0.5[a]		VAN MIC (µg/mL) ≥ 1.0[b]	
	TLV	**VAN**	**TLV**	**VAN**
S. aureus	33 / 37 (89.2%)	22 / 28 (78.6%)	74 / 85 (87.1%)	78 / 105 (74.3%)
MRSA	11 / 12 (91.7%)	12 / 14 (85.7%)	50 / 58 (86.2%)	66 / 88 (75.0%)
MSSA	22 / 25 (88.0%)	10 / 14 (71.4%)	24 / 27 (88.9%)	12 / 17 (70.6%)

Note: Cells show the number of patients with clinical cure divided by the number of patients with the given pathogen.
Note: Only includes patients with single baseline pathogen.
TOC = test of cure; ME = microbiologically evaluable; MIC = minimum inhibitory concentration; TLV = telavancin; VAN = vancomycin; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-sensitive *S. aureus*.
[a] All MICs are 0.5 ug/mL, except for one telavancin patient with MIC ≤ 0.25 ug/mL.
[b] All MICs are 1.0 ug/mL, except for two telavancin patients with MIC = 2.0 ug/mL.

Telavancin demonstrated consistent efficacy and higher cure rates in the treatment of NP across subgroups, including patients at risk for poor outcomes, such as the elderly, patients with bacteremic NP, and patients with high (≥ 20) Acute Physiology and Chronic Health Evaluation (APACHE) II scores, and patients with VAP.

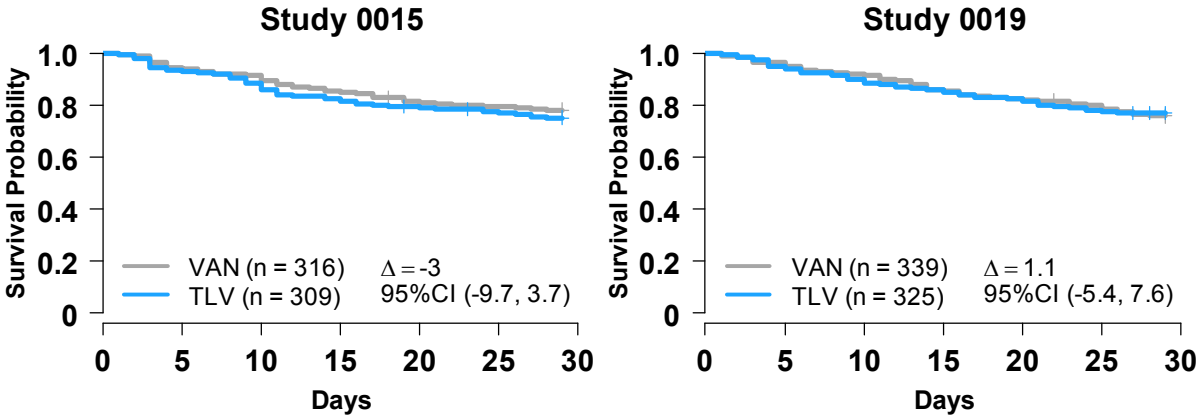
1.2.4 Summary of Post-Hoc Assessment of All-Cause Mortality

As noted in Section 1.2.1, subsequent to the completion of Studies 0015 and 0019 and the planned analysis of the data, Theravance conducted an additional and more extensive analysis of the mortality data from these two studies.

The primary objective of the post-hoc analyses was to examine the noninferiority of telavancin to vancomycin treatment, with respect to all-cause mortality at Day 28, for patients in the AT analysis set who also met the criteria for diagnosis of pneumonia as described in the guidelines of the American Thoracic Society (ATS)/Infectious Disease Society of America (IDSA) (ie, the presence of a new or progressive radiographic infiltrate plus at least two of three clinical features [fever > 38°C, leukocytosis or leukopenia, and purulent secretions]), ie, the AT-ATS/IDSA analysis set.

Noninferiority of telavancin to vancomycin, which was met when the lower bounds of the 95% CI for the difference in mortality (survival) was greater than -0.10, was demonstrated for the post-hoc 28-day all-cause mortality endpoint for each study (Studies 0015 and 0019) and the combination of Studies 0015 and 0019 in the primary analysis set of all-treated patients who met the ATS/IDSA criteria for diagnosis of pneumonia (AT-ATS/IDSA) (Figure 2).

Figure 2: Kaplan-Meier Survival Curves – AT-ATS/IDSA Population, Studies 0015 and 0019



AT = all-treated; ATS = American Thoracic Society; IDSA = Infectious Disease Society of America; VAN = vancomycin; TLV = telavancin; CI = confidence interval.

In addition to the primary analysis set (AT-ATS/IDSA), supportive analysis sets were also defined, ie, patients who had at least one Gram-positive baseline pathogen (including mixed infections), patients with only Gram-positive baseline pathogens, patients with MRSA at baseline (including mixed infections), and patients with only MRSA at baseline.

Various sensitivity analyses included modifications that excluded patients who did not have reliable respiratory samples, who received potentially effective concomitant antibiotics (PEA) with Gram-positive activity, who did not have confirmed chest radiography, or who did not receive adequate Gram-negative coverage for patients with mixed (Gram-positive/Gram negative) infections.

Results for the sensitivity analyses of the primary analysis set that excluded patients who did not have reliable respiratory samples, who received PEA, or who did not have confirmatory chest radiography, tended to favor telavancin with respect to 28-day all-cause mortality. In the supportive microbiologic analysis sets, the mortality rates for telavancin were lower in patients with monomicrobial Gram-positive pathogens, in each study and in the aggregate, and were generally similar to vancomycin in all other supportive analysis sets.

The deaths occurring in Studies 0015 and 0019 were carefully evaluated for evidence of treatment associations, both clinically and statistically. The clinical review resulted in the conclusion that patients who succumbed, regardless of treatment received, had multiple risk factors for mortality, ie, death was not unexpected. The causes of death cited by the investigators were similar between the 2 treatment groups, did not identify pneumonia as the primary cause of death in large numbers of patients in either the vancomycin or telavancin treatment group, and did not indicate evidence of drug toxicity. A potentially important finding is that exclusion of patients who only had Gram-negative pathogens recovered from

baseline cultures resulted in a much smaller difference in the mortality rates between the two groups among patients with baseline CrCL < 30 mL/min.

In summary, noninferiority of telavancin to vancomycin was demonstrated for each study (Studies 0015 and 0019) and the combination of Studies 0015 and 0019 for the post-hoc 28-day all-cause mortality endpoint, and sensitivity analyses identified a target group of patients with the optimal benefit-risk balance.

1.2.5 Summary of Safety

In the Phase 3 clinical studies in NP, the incidence of treatment-emergent adverse events (AEs) in the telavancin treatment group was similar to that in the vancomycin treatment group. Of the 751 patients treated with telavancin, 82% experienced at least one AE compared with 82% of the 752 patients treated with vancomycin. Of patients treated with telavancin, 8% discontinued treatment due to AEs versus 5% of patients who received vancomycin. Serious adverse events (SAEs) were reported in 31% of patients treated with telavancin compared with 26% of patients who received vancomycin. The most frequently reported SAE was septic shock (4% of patients in both treatment groups). Multiorgan failure (MOF), renal failure acute, and sepsis were experienced in slightly more (1% absolute difference) patients treated with telavancin than patients treated with vancomycin. A total of 342 patients died in the Phase 3 NP studies. The difference between treatment groups in the incidence of AEs with an outcome of death was < 1% for all AEs, with the exception of multiorgan failure (telavancin 3%, vancomycin 1%).

The incidence of renal AEs indicative of renal impairment (increased serum creatinine, renal impairment, renal insufficiency, and/or renal failure) was 10% in patients treated with telavancin and 8% in patients treated with vancomycin. Of the patients who had at least one renal AE, 54% in each treatment group recovered completely, recovered with sequelae, or were improving from the renal AE at the last visit. Three percent of patients treated with telavancin and 2% of patients treated with vancomycin experienced at least one renal SAE and renal AEs led to discontinuation of 2% and 1% of patients in the telavancin and vancomycin treatment groups, respectively. Per the investigator's assessment, a total of 5 patients (3 telavancin, 2 vancomycin) died following the development of a renal AE. Each of these patients had some degree of renal impairment at baseline.

In the NP trials, increases in serum creatinine to 1.5 times baseline value occurred more frequently among patients treated with telavancin (16%) compared with patients treated with vancomycin (10%).

There were few corrected QT interval (QTc) outliers (corrected QT interval using Fridericia's correction [QTcF] increase from baseline > 60 msec and/or maximum QTcF value > 500 msec) in the treatment groups, and no apparent clinical consequences as a result of these observations. Many of the NP patients had pre-existing cardiac conditions at baseline, abnormal baseline electrocardiogram (ECG) findings, or both. No morbidity or mortality attributable to QTcF prolongation was reported.

Decline in renal function (estimated CrCL to < 30 mL/min) during treatment among patients with baseline CrCL ≥ 30 mL/min was associated with higher mortality rates in both treatment groups, but the mortality rates were higher in the telavancin group. When this analysis was restricted to patients who only had Gram-positive pathogens at baseline, no difference in mortality was found, even in patients whose renal function declined. This further supports the previously mentioned association of Gram-negative pathogens with worse outcomes, particularly in the telavancin group.

However, patients treated with telavancin should have their renal function monitored carefully, and if renal function declines significantly during treatment, appropriate dosage adjustments should be made, consideration given to continuing telavancin if the anticipated benefit to the patient outweighs the potential risk, or discontinuation of telavancin if other appropriate options for treatment are available.

Overall, the safety profile of telavancin is well-characterized. Approved labeling for telavancin presently includes a warning to avoid use during pregnancy unless the potential benefit to the patient outweighs potential risk to the fetus. In addition, proposed new labeling warns against the use of telavancin in patients with baseline severe renal impairment unless the anticipated benefit outweighs the potential risk.

1.3 Conclusions

- *There is a need for new antibiotics that will effectively treat resistant Gram-positive bacterial strains and that have a low potential for development of resistance.*
- *Telavancin is an effective antibiotic for the treatment of NP due to Gram-positive pathogens, including MRSA.*
- *Noninferiority (10% margin) was demonstrated with two clinical endpoints: (1) clinical response at TOC, and (2) all-cause mortality in the AT-ATS/IDSA population.*
- *In the patient subgroup most likely to respond – patients with only Gram-positive infection – noninferiority was also demonstrated for clinical response and all-cause mortality.*
- *Significantly higher cure rates were observed among patients with only S. aureus infection and in patients with S. aureus infection with higher vancomycin MIC values.*
- *Numerically better cure rates were observed among telavancin-treated patients compared with vancomycin in patients at risk for poor outcomes: the elderly, those who were bacteremic at baseline, those with a high APACHE II score, and patients with VAP.*
- *Subgroup analyses show that the subgroup of subjects with CrCL < 30 mL/min are at increased risk of all-cause mortality. Patients with CrCL < 30 mL/min should only be treated if the anticipated benefit to the patient would outweigh the potential risk.*
- *Renal reserve should be an important consideration in choosing treatment with telavancin. Renal function should be monitored carefully in patients treated with telavancin, and if renal function declines significantly during treatment, appropriate dosage adjustments should be made, consideration given to continuing telavancin if*

the anticipated benefit to the patient outweighs the potential risk, or discontinuation of telavancin if other appropriate options for treatment are available.

2 MEDICAL NEED FOR NEW TREATMENTS OF NOSOCOMIAL PNEUMONIA

2.1 Description of Patients and Disease Burden

Despite advances in antimicrobial therapy, standard care, and the implementation of a broad range of preventive measures, NP, including VAP, remains an important cause of morbidity and mortality (2). Although pneumonia constitutes the second most common nosocomial infection (after urinary tract infection), it is the leading cause of mortality due to hospital-acquired infections. Available data suggest that NP, usually defined as pneumonia occurring 48 hours or more after hospital admission, occurs at a rate of 5 to 10 cases per 1000 hospital admissions, with the incidence increasing by as much as 20-fold in mechanically-ventilated patients. Development of NP increases hospital stay by an average of 7 to 10 days, and is responsible for more than 50% of all antibiotics prescribed in the intensive care unit (ICU). It has been reported to produce an excess cost of more than $40,000 per patient (2).

The incidence of nosocomial infections due to Gram-positive cocci such as *S. aureus*, particularly MRSA, has been dramatically increasing in the US (2, 27, 50). According to data collected from hospitals participating in the National Nosocomial Infections Surveillance (NNIS) system, the proportion of *S. aureus* hospital isolates that were resistant to methicillin, increased from 36% in 1992 to 64% in 2003 (28). In ICU patients with nosocomial infections, MRSA isolates increased by 11% from the interval 1998 to 2002 to 60% in 2003 (8). The increasing rates of multidrug-resistant (MDR) pathogens, particularly MRSA, and their associated morbidity and mortality have created a rising need for new antimicrobial agents with greater potency against such pathogens, as well as maintaining stability to common resistance mechanisms.

2.2 Limitations of Current Therapies

Four antibacterial drugs (ciprofloxacin, levofloxacin, linezolid, and piperacillin/tazobactam) have been approved for the treatment of NP, and vancomycin is approved for pneumonia due to MRSA. Of these drugs, only vancomycin and linezolid have demonstrated reliable in vitro activity against MRSA. Five other antibiotics approved since 2000 for Gram-positive infections (quinupristin/dalfopristin, tigecycline, doripenem, daptomycin, and ceftaroline) are not approved for NP. Therefore, since 2000, no antibiotic has been approved for NP, and the potential for new agents in this indication in the near future is extremely limited.

Although vancomycin has been the treatment of choice for serious infections due to MRSA, its clinical efficacy has been questioned, especially for infections such as complicated bacteremia and endocarditis (10). Although high-level vancomycin resistance remains rare among *S. aureus*, gradual increases in MIC values for MRSA have been documented in many regions of the US (26, 18, 55). Growing proportions of isolates of MRSA have higher vancomycin MICs (1 to 2 µg/mL) and appear to be hVISA (51). Worldwide, an estimated 5% to 15% of MRSA isolates are reported to be hVISA. All-cause mortality has also been reported to increase as a function of vancomycin MIC in MRSA NP, VAP, and health care-associated pneumonia (HCAP) (20).

Linezolid is not an ideal treatment for NP, either as empiric or pathogen specific therapy. It is bacteriostatic and associated with significant drug-drug interactions (including serotonin syndrome associated with coadministration of serotonergic agents and linezolid) as well as myelosuppression, both of which may complicate the care of seriously ill patients. Furthermore, resistance to linezolid has emerged and could become a larger problem (15, 4).

Additional safety and tolerability concerns exist for current treatment options for NP, including nephrotoxicity observed with high doses of vancomycin, and bone marrow suppression observed with linezolid.

2.3 New Alternative Therapy Needed for Nosocomial Pneumonia Due to Gram-Positive Infections

Evidence is accumulating to suggest that early initiation of antibiotic therapy (within 24 hours of the diagnosis) is important (39, 29, 25, 38) and that inappropriate initial antibiotic therapy for patients with NP and VAP is associated with increased mortality (58, 29, 38, 1, 7, 34). Because of the need to initiate treatment immediately and because the causative pathogen(s) are not identified at the time of diagnosis, institution of empiric antibiotic therapy in a patient with NP is typically necessary (2). The selection of empiric antibacterial agents is based on an assessment of the likely causative pathogens, as well as the presence of risk factors for MDR pathogens (2).

The challenge of treating NP is particularly daunting due to the need for an effective initial empiric treatment that covers multiresistant pathogens. To keep ahead of this burgeoning resistance, there is a critical need for new therapies, particularly therapies with limited potential for resistance.

3 DEVELOPMENT AND REGULATORY MILESTONES IN NOSOCOMIAL PNEUMONIA

The design for the two Phase 3 studies (Study 0015 and Study 0019) was based on the July 1998 FDA Guidance for Industry: "Nosocomial Pneumonia – Developing Antimicrobial Drugs for Treatment" and "Developing Antimicrobial Drugs – General Considerations for Clinical Trials" and in accordance with the EMA/CPMP guidance document: "Note for Guidance on Evaluation of Medicinal Products Indicated for Bacterial Infections" CPMP/EWP/558/95 Rev 1, 22 April 2004. The primary outcome variable in Studies 0015 and 0019 was the clinical response at TOC based on investigator assessment at the follow-up visit, 7 to 14 days after the last dose of study drug.

Discussion with the FDA regarding the Phase 3 clinical development program for telavancin for NP took place in July 2004 at an End of Phase 2 meeting. The studies were conducted between early 2005 and mid-2007. The SAP was finalized and submitted to the FDA before the blinded treatment assignments were known and the SAP was subsequently discussed with the FDA at the pre-NDA meeting in March 2008.

The NDA was submitted in January 2009. In June 2009, in responding to a query from Theravance regarding the justification of a noninferiority margin, the Division noted that assessment of the noninferiority of telavancin would depend on the analysis of the all-cause mortality data. The Division referenced discussions at the HAP/VAP workshop conducted in March 2009, but no further direction was provided on this point, including how mortality might be considered, relative to the prespecified primary clinical response study endpoint, in determining whether telavancin should be approved. In response to the increasing interest in all-cause mortality as an outcome measure for NP, Theravance made the decision to return to the clinical sites and collect vital status data through Study Day 49 for each study participant and informed the FDA of the availability of these data.

Theravance received a Complete Response Letter in November 2009. The letter stated that:

- The results of the two Phase 3 clinical trials (Studies 0015 and 0019) did not provide substantial evidence to demonstrate the safety and efficacy of telavancin in the treatment of NP.
- Published historical evidence would only permit interpretation of noninferiority trials for NP and VAP using all-cause mortality as the primary endpoint.
- The two submitted trials were of insufficient size and statistical power to identify a difference in all-cause mortality between telavancin and comparator-treated patient groups if such a difference existed. Differences in the distribution of baseline prognostic factors for mortality across the two trials may preclude pooling; if, upon further review, pooling of the mortality data was determined to be acceptable, the collective all-cause mortality data may only be of sufficient size and statistical power to be considered analogous to one adequately sized trial with a mortality endpoint and additional evidence supporting safety and effectiveness would still be required.

Theravance was advised to:

- Submit all available all-cause mortality data and account for any censored information.
- Provide a scientific rationale for pooling all-cause mortality data across the two clinical trials.

Meetings were held with the FDA to review outstanding issues with the application, in particular, to discuss the recommended approach to the analysis of mortality in NP.

A response to the Complete Response Letter, including the mortality data and re-analysis was resubmitted to the FDA in December 2009.

An Incomplete Response Letter was received in January 2010. The letter noted:

- The pooled mortality data from Studies 0015 and 0019 would equate to only one adequate and well-controlled trial and would not constitute substantial evidence of efficacy.
- The adequacy and similarity of populations across studies for purposes of pooling had not yet been determined, and is a review issue.

A meeting was held with FDA to continue the discussion of issues surrounding the analysis of a mortality endpoint in NP. A response was resubmitted in June 2010 and included reanalyses of the mortality data in Studies 0015 and 0019 that were based on discussions with the FDA.

In November 2010, the FDA issued the draft guidance for "Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment."

Theravance received a second Complete Response Letter in December 2010. The Agency concluded that:

- Studies 0015 and 0019 did not provide substantial evidence to demonstrate the safety and efficacy of telavancin in the treatment of NP. While a substantial amount of missing mortality data was recovered and provided for analysis, the analysis in the population of interest (ie, patients with NP caused by Gram-positive bacteria) in Study 0015 did not demonstrate noninferiority of telavancin relative to vancomycin. When the same analysis population was assessed in Study 0019, the observed treatment difference in 28-day all-cause mortality rates was 2.0% (telavancin: 24.3%; vancomycin: 22.3%) and the upper bound of the 95% CI is 10.0%, (-6.1%, 10.0%), and did not provide sufficient evidence for the noninferiority of telavancin to vancomycin. In addition, the method of selection of patients did not provide adequate assurance that they had the disease being studied due to uncertainties with respect to interpretations of chest radiographs and adequacy of respiratory tract specimens.
- The analysis method that compared telavancin-treated patients from the Phase 3 trials to the historical studies of patients receiving inadequate, inappropriate, and delayed therapy was problematic. Specifically, the baseline characteristics of the patients in the telavancin trial patients were not comparable to those in the historical control groups.
- The pooling of patients across the two Phase 3 trials was not appropriate because patients in Study 0015 had more potential risk factors for mortality (eg, diabetes mellitus and renal impairment/failure) than patients in Study 0019.

- The inclusion of post-hoc-selected prognostic risk factors for mortality in the analyses was not acceptable because they may bias the results.
- The diagnosis of renal failure was left to the discretion of the investigator, and in some cases, it was unclear whether some of the patients may have had acute as well as chronic renal failure. For patients with potential risk factors, renal status should have been more specifically defined by standardized measures at entry and followed more closely for at least 28 days.

The FDA proposed that Theravance conduct two new adequate, well-controlled studies to demonstrate the safety and efficacy of telavancin in patients with NP. A meeting to discuss the complete response was held with the Division and Office of Antimicrobial Products (OAP) representatives.

A request for Formal Dispute Resolution was submitted by Theravance in August 2011. The appeal of action was not accepted by the Director, Office of New Drugs (OND), but Theravance was encouraged to resubmit the application for further review by the Agency and presentation to an Anti-infective Drugs Advisory Committee (AIDAC) meeting. The Director also stated that the Agency background materials and presentations for the meeting would make clear that the guidance for HAP/VAP is not final, and that the Agency is seeking advice on the 'totality of the data' from the current application, noting that the development program was completed before the draft guidance was issued. Subsequently, Theravance met with Division, OAP, and OND representatives to discuss the content of the resubmission and context for an Advisory Committee, following which detailed requests for datasets and analyses were provided by the Agency.

The NDA for telavancin in treatment of patients with NP was resubmitted in July 2012.

4 DEVELOPMENT OF TELAVANCIN IN NOSOCOMIAL PNEUMONIA

4.1 Preclinical Safety Evaluation

To evaluate the potential toxicity of telavancin, the nonclinical program included safety pharmacology studies, single- and multiple-dose toxicity studies of up to 6 months in duration, genotoxicity studies, developmental and reproductive toxicity studies, and ex vivo assays to evaluate the hemolytic potential. Additional studies performed included a 6-week study in male rats to assess potential gonadal toxicity, a 6-week study to evaluate potential for immunotoxicity, studies to assess the potential for local irritation of the skin and eye, and a study to assess the potential of telavancin to cause phototoxicity. This program identified potential effects on cardiac repolarization, renal toxicity, and reproductive toxicity as issues with potential relevance to the clinical use of telavancin.

4.1.1 Renal

The nephrotoxic potential for telavancin has been characterized in dogs and rats in exploratory studies and in repeated-dose studies of up to 6 months in duration.

The renal toxicity observed with telavancin in rats and dogs was relatively mild and showed evidence of reversibility, based on a return towards baseline values for blood urea nitrogen (BUN) and creatinine and a reduction in histopathology severity scores. These effects were detected at exposures (based on area under the concentration-time curve [AUC] values) similar to those measured in clinical studies.

4.1.2 Potential Effects on Cardiac Repolarization

The safety pharmacology program included in vitro receptor binding assays, exploratory and Good Laboratory Practices (GLP) studies on the potential of telavancin to interfere with human ether a-go-go-related gene (hERG) potassium channel currents and action potential duration (APD) in canine and ovine Purkinje fibers, single-dose studies evaluating the potential of telavancin at doses up to 50 mg/kg to cause cardiovascular and respiratory changes in anesthetized dogs, and a multiple-dose study to evaluate potential cardiovascular effects in conscious dogs at doses up to 100 mg/kg/day.

The in vivo assays failed to detect an effect on cardiac repolarization; however, the observation of effects in two of the in vitro studies (hERG and canine Purkinje fiber) suggested that a prolongation of the QTc interval in humans may be possible. The approved label for telavancin for cSSSI includes a precaution when prescribing telavancin to patients taking drugs known to prolong the QT interval (Appendix 2). Additionally, use of telavancin should be avoided in patients with congenital long QT syndrome, known prolongation of the QTc interval, uncompensated heart failure, or severe left ventricular hypertrophy (Appendix 2).

4.1.3 Fetal Development

The safety of telavancin in pregnant women was not evaluated in clinical studies. Because lower fetal weights in rats and a low incidence of limb defects in three species were noted,

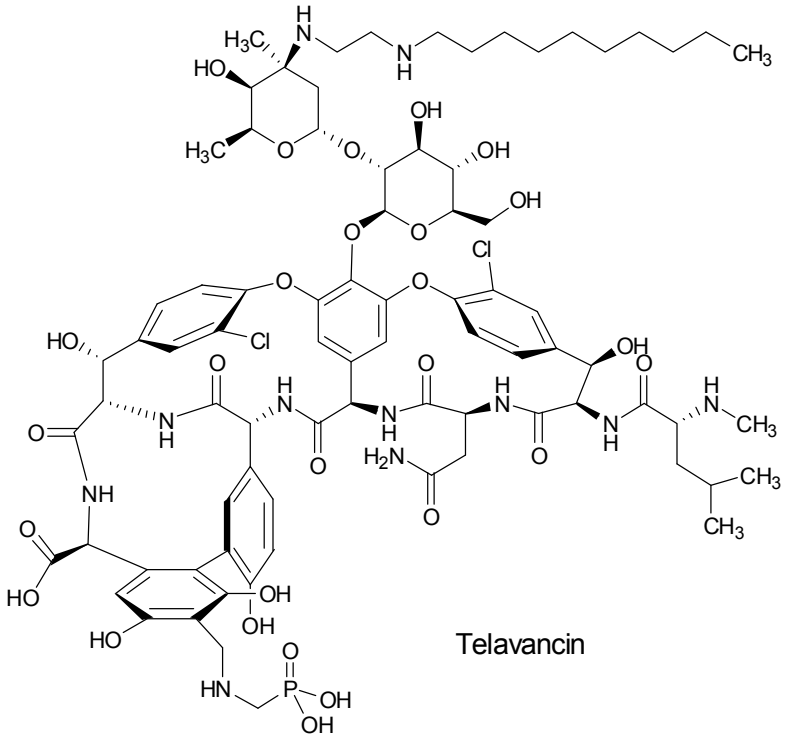
the approved label for telavancin for cSSSI includes a boxed warning about these effects and a classification of Pregnancy Category C, indicating that the drug should be used during pregnancy only if the potential benefit to the patient outweighs potential risk to the fetus (Appendix 2).

4.2 Microbiology

- *Telavancin is a semisynthetic lipoglycopeptide antibiotic active against Gram-positive bacteria.*

Telavancin is a semisynthetic lipoglycopeptide antibiotic active against Gram-positive bacteria, including pathogens commonly associated with NP. In particular, telavancin is active against resistant Gram-positive organisms such as MRSA and MDR *S. pneumoniae*. The chemical structure of telavancin is presented in Figure 3.

Figure 3: Chemical Structure of Telavancin



Telavancin

4.2.1 Mechanism of Action

Telavancin exerts its bactericidal action through a mechanism that combines inhibition of cell wall synthesis and disruption of bacterial membrane function. Telavancin inhibits cell wall synthesis by binding to late-stage peptidoglycan precursors, including lipid II, in a manner similar to vancomycin (24). This activity prevents both the polymerization of precursor into peptidoglycan and subsequent cross-linking events. Relative to vancomycin,

telavancin possesses enhanced affinity for lipid II (6). As a consequence, telavancin is > 10-fold more potent than vancomycin at inhibiting cell wall biosynthesis.

In addition to inhibiting cell wall synthesis, telavancin also binds to the bacterial membrane, disrupting membrane barrier function (24). Vancomycin lacks this mechanism. Binding of telavancin to the bacterial membrane is lipid II dependent. The high affinity of telavancin for lipid II translates into preferential binding to the division septum, the site of active cell wall synthesis (41). Potent inhibition of cell wall synthesis, combined with disruption of bacterial membrane function, results in the enhanced antibacterial potency of telavancin relative to vancomycin.

4.2.2 Resistance Studies

The only known resistance mechanism that affects telavancin activity is VanA-type vancomycin resistance. Non-VanA-type vancomycin-resistant organisms are typically susceptible to telavancin (MIC ≤ 1 µg/mL) (31, 11, 12). There is no other known cross-resistance between telavancin and other classes of antibiotics. Organisms resistant to daptomycin or linezolid remain susceptible to telavancin at the proposed MIC breakpoints. In vitro studies of intrinsic resistance development, including both single-step and multi-passage experiments, suggest that telavancin has a low potential to select for resistance (30). During clinical trials, there was no evidence of resistance developing to telavancin. Of note, there have been no instances of telavancin-resistant strains of *S. aureus* arising in either surveillance studies or clinical use.

4.2.3 In Vitro Spectrum of Activity

The in vitro activity of telavancin has been continually monitored in an international surveillance program since its approval for the treatment of cSSSIs in the US in 2009. Sources of the clinical isolates in this program include specimens from the bloodstream, respiratory tract (including hospitalized patients with pneumonia) and skin and wound sites. To date, more than 40,000 bacterial clinical strains have been tested, including over 8,300 MRSA isolates. This program has demonstrated the potent and consistent in vitro activity of telavancin against the principal species implicated in NP: *S. aureus* (including methicillin-resistant isolates) and *S. pneumoniae* (including penicillin-resistant isolates), as well as against other Gram-positive pathogens. Notably, telavancin activity is consistent irrespective of specimen source or geographic region and MIC distributions are narrow for each of the claimed NP pathogens. A summary of telavancin activity against *S. aureus* and *S. pneumoniae* isolates collected during 2010 is provided in Table 2.

Table 2: In Vitro Activity of Telavancin and Comparator Agents Against *S. aureus* and *S. pneumoniae* Isolates Obtained from Medical Centers in North America, Latin America, Europe, and the Asia-Western Pacific Region in 2010

Organism	No. Tested	Agent	MIC (µg/mL)		
			Range	MIC_{50}	MIC_{90}
S. aureus (oxacillin-S)	4565	Telavancin	0.03−0.5	0.12	0.25
		Vancomycin	≤ 0.25−2	1	1
		Linezolid	≤ 0.12−2	1	2
		Levofloxacin	≤ 0.5−> 4	≤ 0.5	≤ 0.5
		Oxacillin	≤ 0.25−2	0.5	0.5
S. aureus (oxacillin-R)	3088	Telavancin	≤ 0.015−0.5	0.12	0.25
		Vancomycin	0.25−2	1	1
		Linezolid	≤ 0.12−> 8	1	1
S. pneumoniae (penicillin-S)	1330	Telavancin	≤ 0.015−0.12	≤ 0.015	0.03
		Vancomycin	≤ 0.12−1	0.25	0.5
		Linezolid	≤ 0.12−4	1	1
		Levofloxacin	≤ 0.5−> 4	1	1
		Penicillin	≤ 0.03−0.06	≤ 0.03	≤ 0.03
S. pneumoniae (penicillin-NS)	820	Telavancin	≤ 0.015−0.06	≤ 0.015	0.03
		Vancomycin	≤ 0.12− 1	0.25	0.5
		Linezolid	≤ 0.12−2	1	1
		Levofloxacin	≤ 0.5−> 4	1	1
		Penicillin	0.12−> 4	2	4

MIC = minimum inhibitory concentration; S = susceptible; NS = nonsusceptible; R = resistant.

In addition to the international surveillance program, a number of studies have focused specifically on the activity of telavancin against staphylococci with reduced susceptibility to vancomycin (53, 30, 11, 33). Collectively, these studies demonstrated that vancomycin-intermediate *S. aureus* (VISA) and hVISA are susceptible to telavancin at the proposed MIC breakpoint for this organism (1 µg/mL).

4.2.4 Supportive In Vitro Microbiology Studies

4.2.4.1 Bactericidal Activity

Telavancin exerts concentration-dependent bactericidal activity against Gram-positive organisms (36, 37, 46, Theravance Inc. Study Report 06-6424-MCB-10, 2006). Minimum bactericidal concentration (MBC)/MIC ratios were ≤ 4 for the majority of staphylococci tested, including hVISA and VISA strains. Concentration-dependent bactericidal effects were demonstrated in time-kill studies against target organisms including MSSA, MRSA, VISA, and coagulase-negative staphylococci. Against streptococci, including beta-hemolytic species, telavancin was bactericidal at low multiples of the MIC. Telavancin was bacteriostatic at low multiples of the MIC against vancomycin-susceptible enterococci. However, at higher test concentrations telavancin was bactericidal against these organisms.

Telavancin has also been shown to retain bactericidal activity against slowly growing isolates of *S. aureus* in time-kill assays and in an in vitro model of biofilm infection (45, 9, 17). In a model of intracellular *S. aureus* infection, telavancin treatment resulted in > 90%

reduction in bacterial titers (3). The activity of telavancin was superior to that of vancomycin in each of these studies.

4.2.4.2 In Vitro Antimicrobial Interactions

In vitro synergy studies detected no antagonistic interactions between telavancin and class-representative antibiotics, which included aztreonam, piperacillin/tazobactam, imipenem, cefepime, amikacin, trimethoprim/sulfamethoxazole, ciprofloxacin and rifampin (52, Theravance Inc. Study Report 05-6424-MB-02, 2005). Synergistic interactions against *S. aureus*, including MRSA strains, were observed with some beta-lactam agents.

4.2.4.3 Effects of Pulmonary Surfactant on Antimicrobial Activity

Commercially available pulmonary surfactant (Survanta®) had no effect on the in vitro activity of telavancin against *S. aureus* or *S. pneumoniae* (19).

4.2.5 Preclinical Pharmacology

4.2.5.1 Pharmacokinetics and Pharmacodynamics

Pharmacokinetic-pharmacodynamic (PK-PD) studies in the neutropenic mouse thigh infection model suggest that total exposure (AUC_{0-24}/MIC) is the PK parameter that correlates with efficacy (23). An AUC_{0-24}/MIC ratio of 219 was required for a 1-$\log_{10}$ reduction in colony forming unit (CFU)/g against an MRSA strain with an MIC of 1 µg/mL in the neutropenic mouse thigh model. This was the target chosen to generate estimates of the telavancin doses evaluated in Phase 2 and Phase 3 clinical trials of cSSSI. The results from Monte Carlo simulations for a 750 mg dose (approximately 10 mg/kg for average adult body weight) were found to yield target attainment rates ≥ 99% for organisms with MIC values as high as 2 µg/mL (Theravance, Inc. data on file).

4.2.5.2 In Vivo Efficacy in Animal Models of Infection

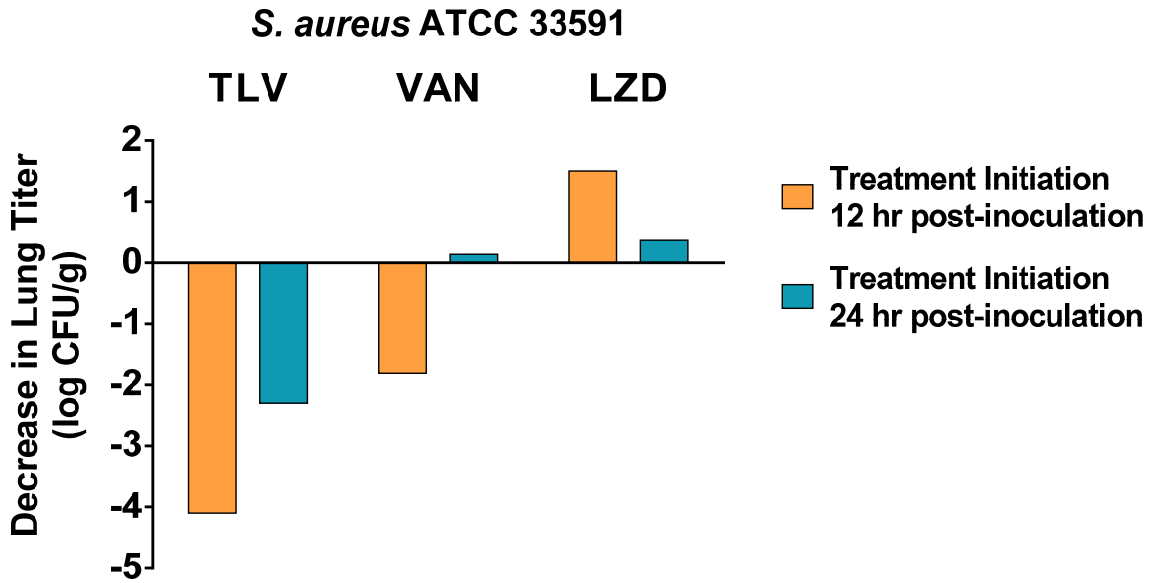
The in vivo antibacterial efficacy of telavancin has been evaluated in a number of animal models of infection caused by Gram-positive pathogens (23, 47, 22, 42, 54, 44, 48, Theravance, Inc. data on file). These studies demonstrated that telavancin was efficacious and displayed dose-dependent bactericidal activity in models of soft tissue (neutropenic mouse thigh, mouse subcutaneous infection), deep seated (rat and rabbit endocarditis), systemic (murine bacteremia), lung (murine pneumonia), and central nervous system (rabbit meningitis) infections. When assessed at human equivalent exposures, telavancin was at least as effective as, and often more effective than comparator agents.

In the neutropenic mouse thigh model of infection, telavancin was efficacious against a variety of Gram-positive pathogens, including *S. aureus*, *S. epidermidis*, *E. faecalis*, and *S. pneumoniae* (23). Telavancin was more potent than nafcillin and vancomycin against *S. aureus* (MSSA) and more potent than vancomycin and linezolid against MRSA. In a high-inoculum variation of the neutropenic mouse thigh infection model with MRSA, telavancin was superior to daptomycin (Theravance Inc. Study Report 04-6424-PH-02,

2004). Telavancin had similar potency against MRSA in models of soft tissue infection in immunocompetent (mouse subcutaneous abscess) and immunocompromised animals (neutropenic mouse thigh). In contrast, vancomycin and especially linezolid were substantially less potent in immunocompromised animals, suggesting that immune status has minimal impact on the efficacy of telavancin (23).

In a murine model of pneumonia, mice were inoculated intranasally with MRSA. Either 12 or 24 hours later, treatment was initiated with human AUC-equivalent doses of one of the three drugs (telavancin, vancomycin, or linezolid). At 48 hours, the animals were sacrificed and lung titers measured. Telavancin was demonstrated to be superior to both vancomycin and linezolid in reducing lung titers over the course of the experiment (Figure 4). Vancomycin was either bacteriostatic or partially bactericidal, and linezolid was minimally bacteriostatic. Telavancin produced > 2 to 4 logs of killing. In a similar experiment evaluating survival in this model over 14 days, telavancin was superior to the other drugs protecting 85 to 90% of the animals over the 14 day period.

Figure 4: Reduction in Lung Titers in the Neutropenic Mouse Pneumonia Model



ATCC = American Type Culture Collection; TLV = telavancin; VAN = vancomycin; LZD = linezolid; CFU = colony forming unit.

4.3 Pharmacokinetics

Details regarding the PK profile of telavancin are provided in the approved label for telavancin for cSSSI (Appendix 2).

4.3.1 Disposition

Telavancin exhibits predictable, linear PK disposition. The PK disposition of IV-administered telavancin was studied in healthy young adults, following single doses from 1 to 15 mg/kg

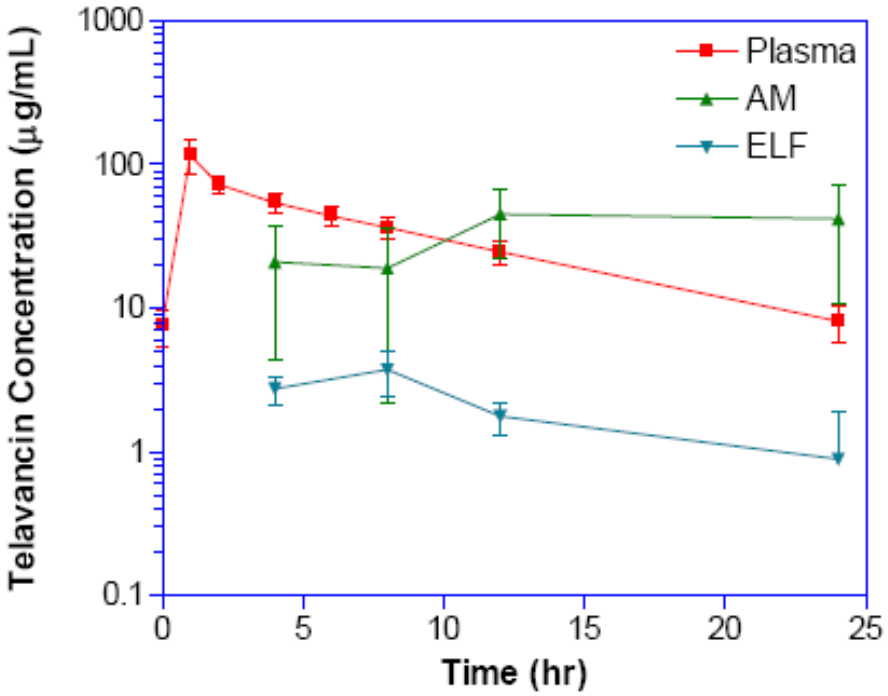
and 7.5 to 15 mg/kg administered once daily for up to 7 days. Steady-state concentrations were achieved by the third daily dose.

The mean PK parameters of telavancin (10 mg/kg) after single and multiple once-daily 60-minute IV infusions are summarized in Appendix 2.

4.3.2 Distribution

Concentrations of telavancin in pulmonary epithelial lining fluid (ELF) and alveolar macrophages (AM) were examined prior to performing clinical studies in NP. Concentrations of telavancin in ELF and AM were measured through collection of bronchoalveolar lavage fluid at various times following administration of telavancin 10 mg/kg once daily for 3 days. On average, telavancin concentrations in ELF and AM exceeded the MIC_{90} (0.5 µg/mL) for clinical isolates of *S. aureus*, including MRSA for the entire 24-hour dosing interval (Figure 5). As noted previously, intracellular telavancin is bactericidal against *S. aureus*.

Figure 5: Steady-State Concentrations of Telavancin 10 mg/kg Administered Intravenously Once Every 24 Hours in ELF and AM



ELF = epithelial lining fluid; AM = alveolar macrophages.

4.3.3 Metabolism

No metabolites of telavancin were detected in in vitro studies using human liver microsomes, liver slices, hepatocytes, and kidney S9 fraction. Additional details regarding metabolism of telavancin is provided in Appendix 2.

4.3.4 Excretion

Telavancin is eliminated primarily by the kidney. In a mass balance study, approximately 76% of the administered dose was recovered from urine and < 1% of the dose was recovered from feces (collected up to 216 hours) based on total radioactivity (Appendix 2).

4.3.5 Special Populations

4.3.5.1 Geriatric Patients

The impact of age on the PK of telavancin was evaluated in healthy young (range, 21 to 42 years) and elderly (range, 65 to 83 years) subjects. The mean CrCL of elderly subjects was 66 mL/min. Age alone did not have a clinically meaningful impact on the PK of telavancin.

4.3.5.2 Pediatric Patients

The PK of telavancin in patients less than 18 years of age has not been established.

4.3.5.3 Sex

The impact of sex on the PK of telavancin was evaluated in healthy male (n = 8) and female (n = 8) subjects. The PK of telavancin was similar in male and female subjects. No dosage adjustment is recommended based on sex.

4.3.5.4 Renal Insufficiency

On the basis of data obtained in a study evaluating 28 subjects with normal renal function (CrCL > 80 mL/min) and subjects with varying degrees of renal impairment following administration of a single dose of telavancin (see Appendix 2), the dosing recommendations shown in Table 3 (which is reproduced from the approved product label) were developed. A second study of nearly identical design was conducted by Astellas Pharma and completed in October 2010 (Study 9809-CL-2403). The results of this investigation confirmed the results of the Theravance study (Study 103a). The effects of peritoneal dialysis have not been studied.

Table 3: Recommended Dosage Adjustment for Telavancin in Adult Patients with Renal Impairment

CrCL (mL/min)[a]	Recommended Telavancin Dosage Regimen
> 50	10 mg/kg every 24 hours
30−50	7.5 mg/kg every 24 hours
10−< 30	10 mg/kg every 48 hours

CrCL = creatinine clearance.
[a] Calculated using the Cockcroft-Gault formula and ideal body weight (IBW). Use actual body weight if < IBW.

For the initial approval for cSSSI, it was determined that there was insufficient information to make specific dosage adjustment recommendations for patients with end-stage renal disease (CrCL < 10 mL/min), including patients undergoing hemodialysis.

4.3.5.5 Hepatic Insufficiency

The PK of telavancin was not altered in subjects with moderate hepatic impairment (n = 8, Child-Pugh B) compared with healthy subjects with normal hepatic function matched for gender, age, and weight. No dosage adjustment is recommended for moderate hepatic impairment (Appendix 2). The PK of telavancin has not been evaluated in patients with severe hepatic impairment (Child-Pugh C).

4.3.6 In Vitro Assessments of Drug Interactions

In vitro studies in human liver microsomes indicate that telavancin minimally inhibits metabolism mediated by the following CYP isoforms: 1A2, 2C9, 2C19, 2D6, and 3A4/5. In addition, because telavancin is not extensively metabolized, clearance of telavancin is not expected to be affected by drugs that inhibit or induce activity of cytochrome P450 isoforms.

4.3.7 In Vivo Assessment of Drug Interactions

4.3.7.1 Effects of Telavancin on Other Drugs

Because CYP 3A4/5 was the most sensitive isozyme in vitro, a clinical study was performed with the probe substrate midazolam.

Midazolam

The results of a study evaluating 16 healthy adult subjects following administration of single doses of telavancin 10 mg/kg, IV midazolam 1 mg, and the two in combination showed that telavancin had no impact on the PK of midazolam and midazolam had no effect on the PK of telavancin. Therefore, telavancin is unlikely to alter the PK of drugs metabolized by the cytochrome P450 system to a clinically significant degree.

4.3.7.2 Interactions of Telavancin with Antibiotics

Drug-drug interaction studies were performed with telavancin and other drugs that are likely to be coadministered (see Appendix 2).

Aztreonam

The results of a study evaluating 11 healthy adult subjects following administration of single IV doses of telavancin 10 mg/kg, aztreonam 2 g, and the two in combination showed that telavancin had no impact on the PK of aztreonam and aztreonam had no effect on the PK of telavancin. No dosage adjustment of telavancin or aztreonam is recommended when the two drugs are coadministered.

Piperacillin/Tazobactam

The results of a study evaluating 12 healthy adult subjects following administration of a single dose of telavancin 10 mg/kg, piperacillin/tazobactam 4.5 g, and the combination of telavancin and piperacillin/tazobactam showed that telavancin had no impact on the PK of piperacillin/tazobactam, and piperacillin/tazobactam had no effect on the PK of telavancin. No dosage adjustment of telavancin or piperacillin/tazobactam is recommended when both drugs are coadministered.

4.3.8 Summary of Pharmacokinetics

Telavancin has linear, predictable PK, with good penetration into potential sites of infection. Its potency and half-life support once daily dosing. Because telavancin is renally excreted, a dosage adjustment is recommended for patients with moderate or severe renal insufficiency.

There is no known potential for drug-drug interactions that could modify the PK of telavancin or affect the disposition of other drugs.

4.4 Program Design – Clinical Efficacy and Safety Studies in Nosocomial Pneumonia

4.4.1 Pivotal Study Design

The Phase 3 NP program included two studies, Studies 0015 and 0019, which were conducted under identical protocols in approximately the same time frame. Each study was a randomized, double-blind, active-controlled, parallel-group, multicenter, multinational trial with a 7- to 21-day treatment period. The randomization was stratified on geographic region, presence or absence of diabetes, and ventilatory status (ventilator-assisted or not). A substantial number of subjects in each study were enrolled in the US. The objective of each study was to demonstrate noninferiority of clinical response with telavancin relative to vancomycin in the treatment of NP due to Gram-positive pathogens, with a focus on infection due to MRSA, and to establish the safety profile of telavancin.

Telavancin was administered at a dose of 10 mg/kg IV once daily. The dosage of telavancin was to be reduced in patients with moderate (CrCL 30−50 mL/min) to severe (CrCL < 30 mL/min) renal insufficiency (Table 3). It should be noted that the clinical trials included patients with baseline CrCL < 10 mL/min, and those randomized to receive telavancin were to be dosed with 10 mg/kg every 48 hours.

Vancomycin was administered at a dose of 1 g IV every 12 hours and dosage adjustments for body weight, renal function, or vancomycin serum level monitoring by unblinded personnel were permitted, according to the standard procedures of each institution.

The studies did not allow “step-down” therapy to oral antibiotics. The primary outcome variable was clinical response, based on investigator assessment, at the follow-up visit 7 to 14 days after the last dose of study drug.

Changes in cardiac repolarization and renal function were detected in preclinical studies, thus the Phase 3 program was designed to further assess the importance of these safety

findings and therefore included patients with renal impairment and also patients receiving drugs known to be associated with QTc prolongation.

Combined, the studies enrolled and treated a total of 1503 patients, 427 of whom had VAP, defined as pneumonia developing after at least 48 hours of mechanical ventilation. As the studies were designed to compare the efficacy of two drugs with activity against Gram-positive pathogens, the use of concomitant Gram-negative therapy was left to the investigator's discretion. However, efforts were made to limit the choices of and duration of treatment with Gram-negative agents.

4.4.2 Diagnosis and Main Criteria for Inclusion

The study entry criteria, the same as those of a previously completed, successful registrational study of linezolid (49), ensured that patients had clinical and radiographic evidence of NP and included patients at risk of poor outcomes, such as the elderly (≥ 65 years) or patients with comorbid conditions such as severe renal impairment (CrCL < 30 mL/min). The only exclusion criteria that limited the severity of illness were related to probability of imminent death (patients were to have been expected to survive for at least 7 days after randomization and could not have had refractory shock or been profoundly neutropenic).

The studies were designed to enroll patients with NP caused by any Gram-positive pathogen. Specifically, an objective of the studies was to assess the effectiveness of telavancin compared with vancomycin against infections due to MRSA. Therefore, it was strongly recommended that patients considered for enrollment have at least one of the following risk factors for MRSA infection:

- Hospitalization within previous 6 months
- Antibiotic treatment (especially fluoroquinolones) within prior 3 months
- At least one chronic illness (especially diabetes)
- Prior infection with MRSA
- Admission from a nursing home or a long term care facility
- Surgical procedure during current hospital stay
- Residence in an area known to have a high prevalence of community-acquired MRSA

Criteria related to patient inclusion in analysis populations are presented in Section 4.4.7.2 for prespecified analyses and in Section 4.5.9.2 for post-hoc analyses of all-cause mortality.

4.4.2.1 Key Inclusion Criteria

To be eligible for inclusion in these studies, patients were required to meet all of the following criteria:

- Male or female patient ≥ 18 years of age

- Clinical signs and symptoms consistent with pneumonia acquired after at least 48 hours of continuous stay in an inpatient acute or chronic-care facility, or acquired within 7 days after being discharged from a hospitalization ≥ 3 days in duration
- At least two of the following signs and symptoms must have been present:
  - Cough
  - Purulent sputum or other deep respiratory specimen
  - Auscultatory findings of pneumonia
  - Dyspnea, tachypnea, or hypoxemia
  - Identification of an organism consistent with a respiratory pathogen isolated from cultures of respiratory tract, sputum, or blood samples

AND

- At least two of the following must also have been present:
  - Fever (> 38°C) or hypothermia (rectal/core temperature < 35°C)
  - Respiratory rate > 30 breaths/min
  - Pulse rate ≥ 120 beats/min
  - Altered mental status
  - Need for mechanical ventilation
  - Elevated total peripheral white blood cell (WBC) count > 10000 cells/mm^3, > 15% immature neutrophils (band forms) regardless of total peripheral WBC count, or leukopenia with total WBC count < 4500 cells/mm^3
- A chest radiograph with findings consistent with a diagnosis of pneumonia (new or progressive infiltrates, consolidation, or pleural effusion) within 48 hours prior to randomization in the study
- Availability of appropriate respiratory or sputum specimens for Gram stain and culture, and venous access for IV dosing
- Willing to receive IV therapy for the duration of treatment
- Informed consent was to be obtained for participation in these studies, as defined by the local Institutional Review Board (IRB)/Ethics Committee (EC)

4.4.2.2 Key Exclusion Criteria

Patients were to be excluded from these studies if they met any of the following criteria:

- Received more than 24 hours of potentially effective systemic (IV/intramuscular [IM] or oral [PO]) antibiotic therapy for Gram-positive pneumonia immediately before randomization (unless documented to have not responded to at least 3 days of treatment or if the isolated pathogen for the current pneumonia was resistant in vitro to previous treatment; per Amendment No. 1). Investigators wishing to enroll patients with renal impairment who had received one or more doses of vancomycin during the last week before enrollment were to contact the Study Physician Helpline to determine eligibility.

- Respiratory tract specimens or sputum with only Gram-negative bacteria seen on Gram stain or culture
- Known infection with MSSA or *S. pneumoniae* that required more than 24 hours of concomitant study medication therapy with an antibiotic for Gram-negative coverage that has activity versus MSSA or *S. pneumoniae* (eg, piperacillin/tazobactam)
- Known or suspected pulmonary disease that precluded evaluation of therapeutic response (eg, granulomatous diseases, lung cancer, or another malignancy metastatic to the lungs); cystic fibrosis or active tuberculosis
- Known or suspected *Legionella pneumophila* pneumonia
- Known or suspected infection with an organism that was not susceptible to medications permitted by the protocol
- Documented or suspected meningitis, endocarditis, or osteomyelitis
- Refractory shock (per Protocol Amendment 1) defined as supine systolic blood pressure < 90 mm Hg for > 2 hours with evidence of hypoperfusion or requirement for high-dose sympathomimetic agents (dopamine ≥ 10 µg/kg/min or norepinephrine ≥ 0.1 µg/kg/min)
- Baseline QTc > 500 msec, congenital long QT syndrome, uncompensated heart failure, or abnormal K+ or Mg++ blood levels that could not be corrected (per Protocol Amendment 1)
- Severely neutropenic (absolute neutrophil count < 500/mm³) or anticipated to develop severe neutropenia during the study treatment period due to prior or planned chemotherapy, or had human immunodeficiency virus (HIV) with CD4+ cell count < 100/mm³ during the last 6 months
- Patients unlikely to survive at least 7 days due to underlying illness

4.4.3 Study Procedures

The study design for Studies 0015 and 0019 is presented in Figure 6. Baseline evaluations were performed before the start of treatment and included pertinent medical history, vital signs (ie, body temperature [oral, tympanic, or rectal], respiratory rate, sputum characterization, cough characterization, and assessment of pleuritic chest pain), an assessment of the signs and symptoms of pneumonia, Gram's stain and culture of respiratory specimens, blood culture, clinical laboratory tests, a chest radiograph or computed tomography (CT) scan, components of the APACHE II score, and three 12-lead ECGs. Sputum or endotracheal aspirate specimens were only considered adequate for culture and diagnosis if they had > 25 polymorphonuclear leukocytes and < 10 squamous epithelial cells per low-power field on Gram-stain microscopy.

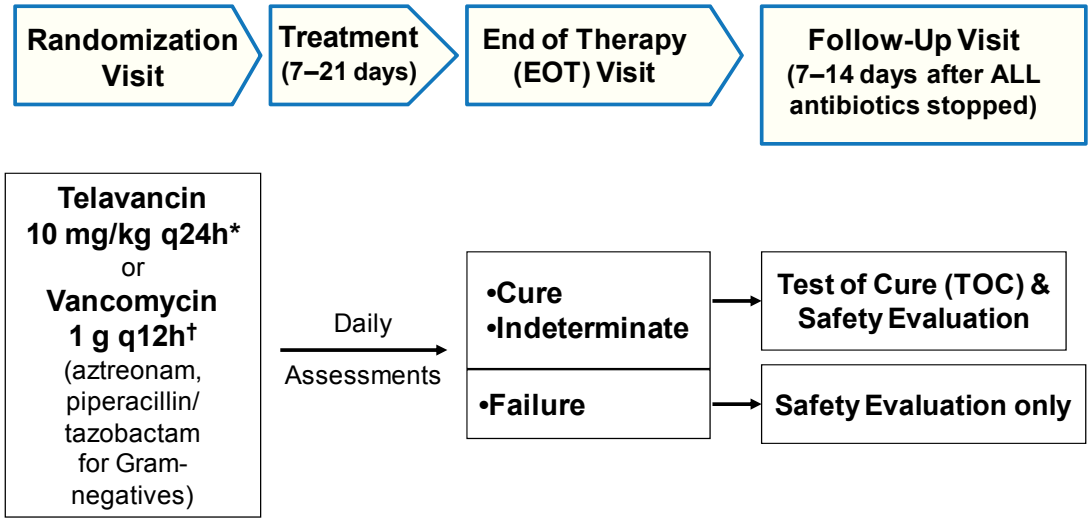
The calendar day of first study medication administration was designated as Day 1; subsequent calendar days were Day 2, Day 3, etc. During the study treatment phase, blinded study medication infusions were administered daily per protocol.

During the treatment phase, patients were evaluated daily for the occurrence of AEs. Additional daily procedures included an assessment of vital signs, the clinical signs and

symptoms of infection, including arterial blood gas measurements (when available), and blood cultures if baseline blood cultures were positive (or if the investigator suspected a bloodstream infection after treatment initiation). Blood samples for clinical laboratory tests were collected every 3 days. On Day 4, three ECGs were obtained and PK sampling was conducted at selected clinical sites.

All patients were to have an end of therapy (EOT) visit within 3 days after the last dose of study medication and a follow-up visit within 7 to 14 days after the EOT visit. A TOC assessment (assessment of signs/symptoms, assessment of clinical response) was conducted at the follow-up visit for patients who had an outcome of cure or an indeterminate outcome at the EOT visit. The investigator determined the clinical response by comparing a patient's signs and symptoms at the EOT or TOC evaluation to those recorded at study admission. Additional procedures at the EOT and TOC evaluations included arterial blood gas measurements (when available), chest radiograph or CT scan (EOT visit only), Gram stain and culture of respiratory specimen (only if clinically indicated), vital signs, assessment of AEs, and collection of clinical laboratory samples for hematology, serum chemistry, and urinalysis.

Figure 6: Study Design, Studies 0015 and 0019



*Dosage adjustment for renal insufficiency per protocol
†Dosage adjustment for weight and/or renal function per institutional policy

Upon a patient's termination of study medication (ie, at the EOT visit), the investigator was to assess the patient's clinical response at EOT as cure, failure, or indeterminate, defined as follows:

- Failure: At least one of the following:
  - Persistence or progression of signs and symptoms of pneumonia that still require antibiotic therapy

  - Termination of study medication due to "lack of efficacy" and initiation within 2 calendar days of therapy with a potentially effective antistaphylococcal medication
  - Death on or after Day 3 attributable to primary infection (as judged by the investigator)
- Cure: Signs and symptoms of pneumonia improved to the point that no further antibiotics for pneumonia were required, and baseline radiographic findings improved or did not progress
- Indeterminate: Inability to determine outcome (for example, Gram-positive antibiotic coverage no longer required, but Gram-negative antibiotic coverage continuing at EOT; only Gram-negative pathogens recovered from baseline cultures)

For all patients randomized into the studies, a follow-up visit was to be conducted 7 to 14 days after the last dose of study medication. However, for the specific case of patients for whom study medication was discontinued but other antibiotics were given to treat pneumonia due to Gram-negative organisms only, the follow-up visit was to be conducted 7 to 14 days after the last dose of ALL antibiotics administered to treat the pneumonia (per Protocol Amendment 1). This allowed for a clinical outcome determination for all patients in the AT population. A blinded TOC assessment was conducted at the follow-up visit only for those patients who were evaluated as a clinical cure or indeterminate at the EOT visit. For purposes of analysis, a clinical response of failure at EOT was carried forward to the TOC evaluation. The blinded evaluation of clinical response was considered adequate to minimize bias, and after discussions with FDA at the End-of-Phase 2 meeting, it was decided that an independent clinical events committee in these studies was not necessary. The investigator was to assess the patient's clinical response at TOC as cure, failure, or indeterminate, defined as follows:

- Failure: At least one of the following:
  - Relapsed pneumonia with the same Gram-positive organism after termination of study medication
  - Death after the end of study medication therapy attributable to primary infection (ie, pneumonia) (as judged by the investigator)
- Cure: Signs and symptoms of pneumonia resolved, and baseline radiographic findings improved or did not progress (see below)
- Indeterminate: Inability to determine outcome

A second posttreatment chest X-ray or CT scan was not required for the follow-up visit, because the assessments were made only for patients who had an EOT assessment of cure or indeterminate (ie, had already demonstrated resolution/nonprogression of radiographic findings and of signs and symptoms). Because clearance of pneumonia, as documented by chest radiographs, may be slower (weeks to months after treatment) than other, more clinically relevant markers (14, 43), the TOC assessment focused on these clinical measures.

4.4.4 Selection of a Comparator Agent

Vancomycin 1 g IV every 12 hours was used in the NP studies as the comparator; this is the FDA-approved dose. The protocol allowed for monitoring of the vancomycin regimen and dosage adjustment based on renal function, body weight, or vancomycin serum level monitoring, according to the institutional policy at each investigative site, by unblinded personnel who were not involved in assessment of patient outcome or care.

Vancomycin was selected as the comparator agent because it is standard empiric therapy for NP, especially in settings where infections with MRSA are prevalent. Vancomycin was also expected to be effective for the treatment of NP caused by other Gram-positive pathogens, including MSSA and *S. pneumoniae* (2). Further, vancomycin has been used as the active comparator in other contemporary registration trials comparing linezolid with vancomycin, each in combination with aztreonam (49,57), and comparing quinupristin/dalfopristin with vancomycin (13). Thus, vancomycin remains the most common standard therapy for this indication.

4.4.5 Study Antimicrobials for MSSA and Concomitant Antimicrobials for Gram-Negative Infections

For patients infected with MSSA, the investigators had the option of using an antistaphylococcal penicillin (ie, IV nafcillin or oxacillin) in place of vancomycin. If the investigator so chose, an order was given by the blinded site investigator, but only carried out for patients randomized to vancomycin by unblinded site personnel. Placebo/dummy infusions were added if the patient had been randomized to telavancin in order to maintain the blind.

For patients with suspected or proven polymicrobial infections involving Gram-negative and/or anaerobic bacteria in addition to the Gram-positive organisms for which study medication were used, aztreonam and/or metronidazole therapy, respectively, was to be added. Piperacillin/tazobactam could be administered for Gram-negative coverage **only** if aztreonam was not appropriate due to an unacceptable level of resistance among Gram-negative bacteria or resistance to aztreonam was documented. However, as piperacillin/tazobactam has activity against MSSA and *S. pneumoniae,* patients with those organisms and no MRSA, who required more than 24 hours of treatment with one of these medications, were not be enrolled. For such patients already enrolled, wherever possible, the piperacillin/tazobactam was to be discontinued or changed to aztreonam as soon as possible. Finally, therapy with metronidazole was to be considered unnecessary if piperacillin/tazobactam was administered, as this agent also has activity against anaerobic bacteria. The original protocol had allowed imipenem for Gram-negative coverage, as well as aztreonam and/or metronidazole therapy; however, imipenem was removed as a treatment option in Protocol Amendment 1.

Because the use of concomitant Gram-negative therapy was left to the investigator's discretion, an assessment of the adequacy of Gram-negative coverage was made by the study medical monitors, after study completion, for patients with mixed Gram-positive and

Gram-negative baseline pathogens. This determination was made while the study medical monitors were blinded to study treatment assignment and outcome.

Gram-negative therapy was considered inadequate if the patient, a) never received antibiotic(s) with in vitro activity covering all Gram-negative pathogens isolated at baseline (ie, never received adequate therapy), or b) did not receive concomitant antibiotic(s) with in vitro activity covering all Gram-negative pathogens isolated at baseline until Study Day 3 or later (ie, inadequate initial therapy). For purposes of these determinations, in the absence of in vitro susceptibility data, a concomitant antibiotic with known Gram-negative activity was deemed active against the baseline Gram-negative pathogen unless the antibiotic was known to routinely not have activity against the baseline pathogen.

To verify these findings, an independent, blinded panel of three external experts in antimicrobial therapy and critical care performed the same adjudication in patients with mixed infection, and the results were similar to the original internal analysis. The external panel's findings revealed slightly higher rates of inadequate Gram-negative therapy with a slightly greater disparity between the treatment groups (higher rates of inadequate coverage in the telavancin group). Therefore, to be conservative, the original adjudication was used for any analyses where this variable was used.

4.4.6 Efficacy and Safety Variables

The prespecified primary efficacy endpoint in Studies 0015 and 0019 was clinical response determined by the investigator at TOC in the AT and CE populations. Other prespecified efficacy parameters included by-pathogen microbiological response at TOC, by-patient microbiological response at TOC, clinical response at EOT, as well as clinical response in predefined subsets of patients, such as those with VAP (early and late), the elderly, and those with varying degrees of renal dysfunction, eg, CrCL < 30 mL/min, bacteremic NP, and by APACHE II score category. The components of the APACHE II score were collected on the case report form, and calculated during data analysis. Missing components were assigned a value of zero.

The principal post-hoc-specified secondary efficacy endpoint was all-cause mortality evaluated 28 days after treatment initiation (see Section 4.5.9).

Safety parameters included death during study, AEs, clinical laboratory test results (hematology, clinical chemistry, urinalysis), and 12-lead ECGs.

4.4.7 Statistical Methods

A SAP was finalized and submitted to FDA before the blind was broken and outcomes were known.

4.4.7.1 Rationale for Aggregation of Studies for Selected Analyses

Both studies are viewed as a representative sample of the NP population due to the underlying heterogeneity of the at-risk population for NP. In aggregate, the results are a

more representative and thus more exhaustive sample of the NP population. These studies, in aggregate, represent the largest study of NP patients to date.

The studies were conducted contemporaneously under identical protocols with the prespecified intent of aggregating study results to draw inferences in MRSA patients where the individual studies would be underpowered. We applied this principle to analyses that are subsets of the larger population.

Given the proposed post-hoc 10% noninferiority margin for the all-cause mortality endpoint, some study populations are underpowered (statistical power less than 80%) (see Section 4.5.9.2). As specified in the protocol for the MRSA population, the intent of aggregation was to be able to draw valid statistical inferences. Theravance conducted intensive and comprehensive exploratory modeling to describe the variation in the current study population for factors that were prognostic for all-cause mortality. It was observed that there were differences in the proportions of patients with some of these post-hoc identified baseline characteristics between studies. There were no differences in the proportions of these baseline characteristics within a study between treatments, except for baseline vasopressor use.

No substantial treatment-by-baseline-characteristic interactions were identified among the baseline characteristics where differences were observed, independent of renal function (Section 4.5.9.2), providing further support that differences in these baseline characteristics did not translate into a differential treatment response.

As there was no systematic bias in the accrual of patients into each study (identical protocol, same approximate time frame, and no bias in assignment of sites to study), the differences in baseline characteristics are considered random effects. As prespecified in the protocols, aggregation of study results is appropriate in selected circumstances in order to draw valid inferences.

4.4.7.2 Definitions of Analysis Populations

Patients who were randomized but did not receive any study medication were not included in the safety and efficacy analyses. The Safety Population comprised those patients who received any study medication. In the Safety Population, patients were grouped according to the treatment (or the predominant treatment, if mixed) actually received. The 4 efficacy analysis populations that were prospectively defined are included in Table 4. These 4 analysis sets were not mutually exclusive; a patient could belong to more than one analysis set. For the efficacy analysis populations, patients were grouped according to the randomization treatment assignment. Criteria used to determine inclusion of patients in the CE population are provided in Appendix 1.

Table 4: Summary of Prospectively Defined Efficacy Analysis Sets

Abbreviation	Name	Definition	Sample Size
AT	All-Treated	All patients who received any amount of study medication	1503 (100.0%)
CE	Clinically Evaluable	Patients in the AT analysis set whose adherence to protocol expectations made it reasonable to infer that his/her clinical outcome reflected the effect of study medication	654 (43.5%)
MAT	Modified All-Treated	Patients in the AT analysis set who also had a baseline pathogen identified	1089 (72.5%)
ME	Microbiologically Evaluable	Patients in the CE analysis set who also had a Gram-positive baseline respiratory pathogen	480 (31.9%)

AT = all-treated; CE = clinically evaluable; MAT = modified all-treated; ME = microbiologically evaluable.

The primary analysis set defined for the post-hoc mortality analysis (see Section 4.5.9.2) was the AT-ATS/IDSA analysis set, which included patients in the AT analysis set who met ATS/IDSA pneumonia criteria. These criteria are included in the proposed inclusion criteria for clinical trials of hospital-acquired bacterial pneumonia (HABP)/ventilator-associated bacterial pneumonia (VABP) in the 2010 Draft FDA Guidance. Additionally, they are included in the ATS/IDSA consensus guidelines for the diagnosis of pneumonia to identify patients who should be treated with antibiotics, offering the optimal balance of sensitivity and specificity in making the diagnosis. The latter consideration is most important given the relatively low sensitivity of the all-cause mortality endpoint in detecting treatment effects of antibiotics in NP, wherein mortality attributable to the infection under study may be very low (~1 to 2%) (5).

4.4.7.3 Efficacy Analysis

The primary efficacy analysis for each of the two studies was a test for noninferiority of telavancin to vancomycin with respect to clinical response at the TOC assessment. For purposes of assessing clinical noninferiority, the tests in the AT and CE populations were considered coprimary. The efficacy analysis was to test for the clinical noninferiority of telavancin relative to vancomycin, employing a noninferiority margin criterion of 20%. Proof of noninferiority was defined as the lower bound of the 95% CI for the difference in cure rates (telavancin – vancomycin) being greater than -20%. The CIs on the between-treatment differences were obtained using asymptotic approximations. The margin was consistent with other contemporary registrational trials in the indication.

For the aggregate analysis of Studies 0015 and 0019, the point estimates and CIs for the treatment differences were obtained using asymptotic methods, stratifying by study. These were calculated using the extended Mantel-Haenszel approach. To test for superiority of telavancin versus vancomycin in patients with MRSA from the aggregate population, statistical significance was declared at the 1-sided 0.025 level. The analysis was to employ asymptotic normal theory methods and was to stratify on study.

Details regarding the primary post-hoc mortality analyses are presented in Section 4.5.9.2.

4.4.7.4 Safety Analysis

AEs were tabulated and summarized according to the Medical Dictionary for Regulatory Activities (MedDRA®, Version 6.1). Continuous laboratory measurements were displayed using summary statistics (mean, median, etc) by treatment group and visit. Observed values and changes from baseline were summarized. Continuous laboratory measurements were also summarized in terms of values relative to lab normal ranges (ie, high, normal, low) in a pre- to post-treatment shift table (eg, normal to high) at each visit. In addition, the number (%) of patients in each treatment group who exhibited a potentially clinically significant (PCS) laboratory change, as defined by prospectively identified criteria, was summarized.

For QTc interval (Fridericia [primary analysis; QTcF] and Bazett [QTcB] – corrected) and QT, the triplicate measurements at each nominal assessment time were averaged to obtain a single analysis value for each assessment time. On-treatment average change and on-treatment maximum changes were summarized using summary statistics (mean, median, etc), and were statistically tested for within- and between-group significance. In addition, for QTc interval, on-treatment maximum values and on-treatment maximum change were summarized by the number and percentage of patients with maximum values ≤ 450, > 450 to ≤ 480, > 480 to ≤ 500, and > 500 msec, and by the number and percentage of patients with maximum increases ≤ 30, > 30 to ≤ 60, and > 60 msec.

Additionally, AEs in the Cardiac Disorder system order class (SOC) were summarized for patients with extreme QTcF changes (ie, > 60 msec maximum increase from baseline or > 500 msec maximum value).

4.5 Efficacy Results

The safety and efficacy studies of telavancin in NP (Studies 0015 and 0019) enrolled a total of 1503 adult patients. Of these, 2 patients in Study 0019, who were randomized to vancomycin, were inadvertently given telavancin. For the efficacy analysis, these 2 patients are included in the vancomycin population (ie, as randomized).

4.5.1 Data Sets Analyzed

In each study, the treatment groups were similar with regard to the percentage of patients included in each of the 4 efficacy analysis populations (AT, MAT, CE, and ME; defined in Section 4.4.7.2), except for the CE population in Study 0015, which consisted of a smaller percentage of patients in the telavancin group than in the vancomycin group (Table 5). A greater percentage of patients in Study 0019 were included in the MAT population than in Study 0015; however, in each study the MAT population was balanced between the treatment groups. Of the 1503 patients in the AT population, 654 (44%) patients were CE and 480 (32%) were ME (patients who were CE and had a Gram-positive pathogen isolated at baseline).

In both studies, the vast majority of patients in both the MAT and ME populations had pathogens recovered from the respiratory tract. A very small proportion of patients had pathogens recovered only from blood. The post-hoc analysis sets are discussed in Section 4.5.9.2.

Table 5: Analysis Populations – Studies 0015 and 0019

	Number of Patients					
	0015		0019		Total	
	TLV (N = 372)	VAN (N =374)	TLV (N = 377)	VAN (N = 380)	TLV (N = 749)	VAN (N = 754)
AT	372 (100%)	374 (100%)	377 (100%)	380 (100%)	749 (100%)	754 (100%)
MAT	257 (69%)	247 (66%)	303 (80%)	282 (74%)	560 (75%)	529 (70%)
Respiratory Pathogens	249 (97%)	245 (99%)	297 (98%)	279 (99%)	546 (98%)	524 (99%)
Blood Pathogens Only	8 (3%)	2 (< 1%)	6 (2%)	3 (1%)	14 (3%)	5 (< 1%)
CE	141 (38%)	172 (46%)	171 (45%)	170 (45%)	312 (42%)	342 (45%)
ME	108 (29%)	113 (30%)	135 (36%)	124 (33%)	243 (32%)	237 (31%)
Respiratory Pathogens	105 (97%)	113 (100%)	134 (99%)	123 (99%)	239 (98%)	236 (100%)
Blood Pathogens Only	3 (3%)	0	1 (< 1%)	1 (< 1%)	4 (2%)	1 (< 1%)
ME as % of CE Population	77%	66%	79%	73%	78%	69%

Note: MAT, CE, and ME percentages were calculated relative to the number in the AT population.
AT = all-treated; TLV = telavancin; VAN = vancomycin; CE = clinically evaluable; MAT = modified all-treated; ME = microbiologically evaluable.

4.5.2 Demographics and Baseline Characteristics

The demographic characteristics of the patient population were well balanced between the two treatment groups (Table 6). There were more patients in the telavancin group than in the vancomycin group with acute renal failure (ARF) (12% vs 9%) and acute lung injury (ALI) (9% vs 5%); however, there were more vancomycin patients than telavancin patients who were on vasopressors (12% vs 8%). The observed signs and symptoms and chest radiographs were consistent with a diagnosis of NP. Approximately one-third of patients had radiographic evidence of pleural effusion and more than half exhibited multilobar infiltrates. Approximately 27% of patients met the definition of having VAP (ie, development of pneumonia after being ventilated for > 48 hours). Nearly 60% were in the ICU at baseline and the mean APACHE II scores were approximately 16. More than one-half of the patients had received > 24 hours of prior antibiotic therapy.

Table 6: Demographic and Baseline Characteristics – AT Population, Studies 0015 and 0019

	Number of Patients						
	0015		0019		Total		
	TLV (N = 372)	VAN (N = 374)	TLV (N = 377)	VAN (N = 380)	TLV (N = 749)	VAN (N = 754)	p-value*
Age (Years)							
Mean ± SD	63 ± 19.2	64 ± 17.3	61 ± 17.8	62 ± 18.0	62 ± 18.5	63 ± 17.7	0.395
≥ 65 Years	202 (54%)	212 (57%)	195 (52%)	196 (52%)	397 (53%)	408 (54%)	0.679
≥ 75 Years	131 (35%)	124 (33%)	99 (26%)	109 (29%)	230 (31%)	233 (31%)	0.955
Sex (n)							
Female	137 (37%)	161 (43%)	125 (33%)	124 (33%)	262 (35%)	285 (38%)	0.261
Race (n)							
White	267 (72%)	272 (73%)	248 (66%)	254 (67%)	515 (69%)	526 (70%)	0.684
Black, of African Heritage	10 (3%)	14 (4%)	15 (4%)	6 (2%)	25 (3%)	20 (3%)	
Asian	91 (24%)	87 (23%)	81 (21%)	91 (24%)	172 (23%)	178 (24%)	
Other (Include Multiple Race)	4 (1%)	1 (< 1%)	33 (9%)	29 (8%)	37 (5%)	30 (4%)	
Medical History							
Diabetes	118 (32%)	114 (30%)	85 (23%)	77 (20%)	203 (27%)	191 (25%)	0.446
Congestive Heart Failure	71 (19%)	78 (21%)	59 (16%)	63 (17%)	130 (17%)	141 (19%)	0.503
COPD	86 (23%)	90 (24%)	87 (23%)	88 (23%)	173 (23%)	178 (24%)	0.855
Chronic Renal Failure	32 (9%)	35 (9%)	11 (3%)	17 (4%)	43 (6%)	52 (7%)	0.397
Shock	14 (4%)	23 (6%)	15 (4%)	18 (5%)	29 (4%)	41 (5%)	0.178
ARDS	24 (6%)	20 (5%)	9 (2%)	10 (3%)	33 (4%)	30 (4%)	0.701
ALI (but not ARDS)	33 (9%)	20 (5%)	18 (5%)	13 (3%)	51 (7%)	33 (4%)	0.043
ICU							
ICU at Baseline	224 (60%)	216 (58%)	207 (55%)	224 (59%)	431 (58%)	440 (58%)	0.754
Vasopressors/Inotropics[a]							
Use of Vasopressors/ Inotropics	30 (8%)	44 (12%)	24 (6%)	45 (12%)	54 (7%)	89 (12%)	0.003
Baseline Renal Status							
CrCL ≤ 50 mL/min	146 (39%)	145 (39%)	109 (29%)	105 (28%)	255 (34%)	250 (33%)	0.743
CrCL < 30 mL/min	61 (16%)	51 (14%)	38 (10%)	41 (11%)	99 (13%)	92 (12%)	0.607
Acute Renal Failure	43 (12%)	35 (9%)	30 (8%)	29 (8%)	73 (10%)	64 (8%)	0.421
Hemodialysis	11 (3%)	9 (2%)	3 (< 1%)	5 (1%)	14 (2%)	14 (2%)	1.000
APACHE II[b]							
Mean ± SD	15 ± 6.2	15 ± 6.1	15 ± 5.9	16 ± 6.3	15 ± 6.1	16 ± 6.2	0.114

Table 6: Demographic and Baseline Characteristics – AT Population, Studies 0015 and 0019

	Number of Patients						
	0015		0019		Total		
	TLV (N = 372)	VAN (N = 374)	TLV (N = 377)	VAN (N = 380)	TLV (N = 749)	VAN (N = 754)	p-value*
Type of Pneumonia							
VAP	103 (28%)	100 (27%)	113 (30%)	111 (29%)	216 (29%)	211 (28%)	0.732
Late VAP (≥ 4 Days on Ventilation at Diagnosis)	91 (24%)	81 (22%)	98 (26%)	90 (24%)	189 (25%)	171 (23%)	0.251
PaO^2/FiO^2 (Mean ± SD)	254 ± 105.8	229 ± 97.9	254 ± 170.4	257 ± 144.9	254 ± 142.4	244 ± 125.3	0.694
NVAHAP	269 (72%)	274 (73%)	264 (70%)	269 (71%)	533 (71%)	543 (72%)	0.732
Sign of Pneumonia							
Fever (Temp > 38°C)	266 (72%)	251 (67%)	292 (77%)	301 (79%)	558 (74%)	552 (73%)	0.597
WBC > 10000/mm³ [c]	218 (68%)	200 (66%)	194 (62%)	208 (63%)	412 (65%)	408 (65%)	0.953
Purulent Secretions	332 (89%)	344 (92%)	345 (92%)	361 (95%)	677 (90%)	705 (94%)	0.029
Heart Rate > 120/min	78 (21%)	79 (21%)	61 (16%)	65 (17%)	139 (19%)	144 (19%)	0.792
Respiratory Rate > 30/min	144 (39%)	137 (37%)	98 (26%)	109 (29%)	242 (32%)	246 (33%)	0.912
SIRS[d]	312 (84%)	311 (83%)	312 (83%)	321 (84%)	624 (83%)	632 (84%)	0.835
Radiological Characteristics							
Multilobar Involvement	238 (64%)	229 (61%)	235 (62%)	231 (61%)	473 (63%)	460 (61%)	0.396
Pleural Effusion	125 (34%)	132 (35%)	112 (30%)	112 (29%)	237 (32%)	244 (32%)	0.782
Prior Antibiotic Use (> 24 Hrs Prior to Enrollment)							
Used Prior Antibiotic (> 24 Hrs)	181 (49%)	209 (56%)	210 (56%)	218 (57%)	391 (52%)	427 (57%)	0.088
Pathogen Resistant to Prior Antibiotic Therapy	34 (9%)	41 (11%)	58 (15%)	61 (16%)	92 (12%)	102 (14%)	0.935
Failed Prior Antibiotic Therapy for NP	88 (24%)	86 (23%)	127 (34%)	125 (33%)	215 (29%)	211 (28%)	0.123
Pneumonia Occurred Despite Prior Antibiotics	92 (25%)	110 (29%)	97 (26%)	98 (26%)	189 (25%)	208 (28%)	0.944

* Fisher's exact test for character variables; 2-sided Wilcoxon test for continuous variables.

AT = all-treated; TLV = telavancin; VAN = vancomycin; SD = standard deviation; COPD = chronic obstructive pulmonary disease; CrCL = creatinine clearance; ARDS = acute respiratory distress syndrome; ALI = acute lung injury; ICU = intensive care unit; APACHE = Acute Physiology and Chronic Health Evaluation; VAP = ventilator-associated pneumonia; NVAHAP = non–ventilator-associated hospital-acquired pneumonia; Temp = temperature; WBC = white blood cell; SIRS = Systemic Inflammatory Response Syndrome; NP = nosocomial pneumonia.

[a] Use of dopamine, norepinephrine, dobutamine, epinephrine, or phenylephrine.

[b] Components with missing value were converted to 0.

[c] Denominator included only patients with a baseline WBC result.

[d] SIRS: patients presented with two or more of the following criteria: 1) temperature > 38ºC or < 36ºC, 2) heart rate > 90 beats/minute, 3) respiration > 20/min or $PaCO_2$ < 32 mmHg, 4) leukocyte count > 12000/mm^3 or < 4000/mm^3, or > 10% immature (band) cells.

4.5.3 Baseline Pathogens

A pulmonary specimen or sputum for Gram-stain and culture and two independent blood specimens were obtained at baseline. A baseline pathogen was defined as an organism known to cause pneumonia identified from the baseline respiratory culture from sputum, endotracheal aspirate (ETA), blind bronchial suctioning (BBS), bronchoalveolar lavage

(BAL), mini-BAL, or protected specimen brush (PSB). If baseline respiratory cultures did not identify a respiratory pathogen (or if baseline respiratory cultures were not available), then an organism known to cause pneumonia that was identified from baseline blood cultures was considered a baseline pathogen.

A sputum sample was considered adequate if it had > 25 polymorphonuclear leukocytes and < 10 squamous epithelial cells (SEC) per field at 100× magnification (low-power, 10× objective). Alternatively, based on supportive literature (56), sputum samples could also be considered reliable if they had < 10 SEC per field, the same criteria for reliable endotracheal aspirates. If a patient had unreliable respiratory samples, but grew a respiratory pathogen from baseline blood cultures, then that patient was considered to have had a reliable sample.

In Table 7 and Table 8, the most common respiratory tract pathogens isolated at baseline from the respiratory tract and from blood cultures, respectively, are summarized by Gram stain and number of pathogens for the MAT population in Studies 0015 and 0019.

Baseline Respiratory Tract Pathogens

Approximately 98% of all MAT patients had a pathogen isolated from the respiratory tract at baseline (Table 7) (the remainder of the MAT patients are those who had a pathogen isolated from only blood cultures at baseline, and are described in the next subsection). The majority had Gram-positive pathogens, and approximately half of patients had Gram-positive pathogens only. Two-thirds of patients had only a single pathogen isolated. In the MAT population, 26% of patients in the telavancin group and 27% of patients in the vancomycin group had Gram-negative pathogens only isolated from respiratory tract cultures.

The aggregate treatment groups were well-balanced in terms of the number and type of respiratory pathogens, as well as the frequency of each pathogen identified. The majority of patients had *S. aureus* isolated at baseline, and treatment groups were similar in the proportion of patients with *S. aureus* infection. Approximately two-thirds of all *S. aureus* were MRSA.

Pathogens Isolated From Baseline Blood Cultures

Approximately 9% of all MAT patients had a pneumonia-causing pathogen isolated from blood cultures at baseline (Table 8). The treatment groups were well-balanced in regard to the number of patients with positive blood cultures. The majority of patients had Gram-positive pathogens, of which *S. aureus* was most common.

Table 7: Most Common Respiratory Pathogens at Baseline – MAT Population, Studies 0015 and 0019

	Number of Patients					
	0015		0019		Total	
	TLV (N = 257)	VAN (N = 247)	TLV (N = 303)	VAN (N = 282)	TLV (N = 560)	VAN (N = 529)
Any Respiratory Tract Pathogen	249 (96.9%)	245 (99.2%)	297 (98.0%)	279 (98.9%)	546 (97.5%)	524 (99.1%)
Pathogen Isolated from Respiratory Tract Only	229 (89%)	228 (92%)	283 (93%)	257 (91%)	512 (91%)	485 (92%)
Pathogen Isolated from Both Respiratory Tract and Blood	20 (8%)	17 (7%)	14 (5%)	22 (8%)	34 (6%)	39 (7%)
Gram-Positive Pathogens	181 (70%)	178 (72%)	220 (73%)	205 (73%)	401 (72%)	383 (72%)
S. aureus	168 (65.4%)	170 (68.8%)	199 (65.7%)	178 (63.1%)	367 (65.5%)	348 (65.8%)
- MRSA	111 (43.2%)	113 (45.7%)	117 (38.6%)	117 (41.5%)	228 (40.7%)	230 (43.5%)
- MSSA	61 (23.7%)	57 (23.1%)	83 (27.4%)	63 (22.3%)	144 (25.7%)	120 (22.7%)
S. pneumoniae	15 (5.8%)	7 (2.8%)	14 (4.6%)	23 (8.2%)	29 (5.2%)	30 (5.7%)
Gram-Negative Pathogens	118 (46%)	111 (45%)	171 (56%)	155 (55%)	289 (52%)	266 (50%)
Pseudomonas aeruginosa	43 (16.7%)	36 (14.6%)	67 (22.1%)	56 (19.9%)	110 (19.6%)	92 (17.4%)
Acinetobacter calcoaceticus	15 (5.8%)	18 (7.3%)	41 (13.5%)	34 (12.1%)	56 (10.0%)	52 (9.8%)
Klebsiella pneumoniae	14 (5.4%)	19 (7.7%)	26 (8.6%)	34 (12.1%)	40 (7.1%)	53 (10.0%)
Escherichia coli	18 (7.0%)	7 (2.8%)	18 (5.9%)	11 (3.9%)	36 (6.4%)	18 (3.4%)
Haemophilus influenzae	15 (5.8%)	9 (3.6%)	10 (3.3%)	8 (2.8%)	25 (4.5%)	17 (3.2%)
Stenotrophomonas maltophilia	8 (3.1%)	8 (3.2%)	18 (5.9%)	6 (2.1%)	26 (4.6%)	14 (2.6%)
Enterobacter cloacae	6 (2.3%)	9 (3.6%)	12 (4.0%)	9 (3.2%)	18 (3.2%)	18 (3.4%)
Proteus mirabilis	5 (1.9%)	9 (3.6%)	5 (1.7%)	6 (2.1%)	10 (1.8%)	15 (2.8%)
Serratia marcescens	7 (2.7%)	3 (1.2%)	4 (1.3%)	4 (1.4%)	11 (2.0%)	7 (1.3%)
Acinetobacter baumanii	3 (1.2%)	2 (0.8%)	4 (1.3%)	4 (1.4%)	7 (1.3%)	6 (1.1%)
Klebsiella oxytoca	2 (0.8%)	2 (0.8%)	3 (1.0%)	6 (2.1%)	5 (0.9%)	8 (1.5%)
Enterobacter aerogenes	3 (1.2%)	2 (0.8%)	3 (1.0%)	2 (0.7%)	6 (1.1%)	4 (0.8%)
Pathogens by Gram Type						
Gram-Positive Pathogens Only	131 (51%)	134 (54%)	126 (42%)	124 (44%)	257 (46%)	258 (49%)
Single Pathogen	121 (47%)	127 (51%)	120 (40%)	115 (41%)	241 (43%)	242 (46%)
Multiple Pathogens	10 (4%)	7 (3%)	6 (2%)	9 (3%)	16 (3%)	16 (3%)
Gram-Negative Pathogens Only	68 (26%)	67 (27%)	77 (25%)	74 (26%)	145 (26%)	141 (27%)
Single Pathogen	56 (22%)	53 (21%)	57 (19%)	56 (20%)	113 (20%)	109 (21%)
Multiple Pathogens	12 (5%)	14 (6%)	20 (7%)	18 (6%)	32 (6%)	32 (6%)
Mixed Gram-Positive/Gram-Negative Infection	50 (19%)	44 (18%)	94 (31%)	81 (29%)	144 (26%)	125 (24%)

Table 7: Most Common Respiratory Pathogens at Baseline – MAT Population, Studies 0015 and 0019

	Number of Patients					
	0015		0019		Total	
	TLV (N = 257)	VAN (N = 247)	TLV (N = 303)	VAN (N = 282)	TLV (N = 560)	VAN (N = 529)
Number of Pathogens						
1 Pathogen	177 (71%)	180 (73%)	177 (60%)	171 (61%)	354 (65%)	351 (67%)
2 Pathogens	48 (19%)	50 (20%)	89 (30%)	85 (30%)	137 (25%)	135 (26%)
3 Pathogens	19 (8%)	11 (4%)	20 (7%)	19 (7%)	39 (7%)	30 (6%)
4 or More Pathogens	5 (2%)	4 (2%)	11 (4%)	4 (1%)	16 (3%)	8 (2%)

Note: More than one pathogen may have been present in any patient.
MAT = modified all-treated; TLV = telavancin; VAN = vancomycin; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-sensitive *S. aureus*.

Table 8: Pathogens Causing Pneumonia Isolated From Baseline Blood Cultures – MAT Population, Studies 0015 and 0019

	Number of Patients					
	0015		0019		Total	
	TLV (N = 257)	VAN (N = 247)	TLV (N = 303)	VAN (N = 282)	TLV (N = 560)	VAN (N = 529)
Any Pathogen Causing Pneumonia Isolated from Blood Cultures	28 (11%)	19 (8%)	20 (7%)	25 (9%)	48 (9%)	44 (8%)
Pathogen Isolated from Both Respiratory Tract and Blood Cultures	20 (8%)	17 (7%)	14 (5%)	22 (8%)	34 (6%)	39 (7%)
Pathogen Isolated from Blood Cultures Only	8 (3%)	2 (< 1%)	6 (2%)	3 (1%)	14 (3%)	5 (< 1%)
Gram-Positive Pathogens	24 (9%)	15 (6%)	14 (5%)	18 (6%)	38 (7%)	33 (6%)
S. aureus	20 (8%)	12 (5%)	12 (4%)	17 (6%)	32 (6%)	29 (5%)
- MRSA	12 (5%)	9 (4%)	7 (2%)	11 (4%)	19 (3%)	20 (4%)
- MSSA	8 (3%)	3 (1%)	5 (2%)	6 (2%)	13 (2%)	9 (2%)
Gram-Negative Pathogens	5 (2%)	5 (2%)	7 (2%)	9 (3%)	12 (2%)	14 (3%)
Pseudomonas aeruginosa	0	1 (< 1%)	2 (< 1%)	1 (< 1%)	2 (< 1%)	2 (< 1%)
Serratia marcescens	0	0	2 (< 1%)	0	2 (< 1%)	0
Acinetobacter calcoaceticus	1 (< 1%)	0	1 (< 1%)	1 (< 1%)	2 (< 1%)	1 (< 1%)
Escherichia coli	2 (< 1%)	1 (< 1%)	1 (< 1%)	0	3 (< 1%)	1 (< 1%)
Proteus mirabilis	0	0	1 (< 1%)	0	1 (< 1%)	0
Burkholderia cepacia	0	0	0	1 (< 1%)	0	1 (< 1%)
Enterobacter cloacae	0	0	0	1 (< 1%)	0	1 (< 1%)
Haemophilus influenzae	0	1 (< 1%)	0	1 (< 1%)	0	2 (< 1%)
Klebsiella oxytoca	1 (< 1%)	0	0	0	1 (< 1%)	0
Klebsiella pneumoniae	1 (< 1%)	1 (< 1%)	0	5 (2%)	1 (< 1%)	6 (1%)
Stenotrophomonas maltophilia	0	1 (< 1%)	0	0	0	1 (< 1%)
Pathogens by Gram Type						
Gram-Positive Pathogens Only Isolated from Blood	23 (9%)	14 (6%)	13 (4%)	16 (6%)	36 (6%)	30 (6%)
Gram-Negative Pathogens Only Isolated from Blood	4 (2%)	4 (2%)	6 (2%)	7 (2%)	10 (2%)	11 (2%)
Mixed Gram-Positive/Gram-Negative Pathogens Isolated from Blood	1 (< 1%)	1 (< 1%)	1 (< 1%)	2 (< 1%)	2 (< 1%)	3 (< 1%)
Number of Pathogens						
Single Pathogen Isolated from Blood	7 (3%)	1 (< 1%)	6 (2%)	3 (1%)	13 (2%)	4 (< 1%)
Multiple Pathogens Isolated from Blood	21 (8%)	18 (7%)	14 (5%)	22 (8%)	35 (6%)	40 (8%)

Note: More than one pathogen may have been present in any patient.
MAT = modified all-treated; TLV = telavancin; VAN = vancomycin; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-sensitive *S. aureus*.

4.5.3.1 Baseline Pathogens Identified as hVISA

A total of 408 MRSA isolates from patients in the NP studies were screened and tested according to the following criteria: VAN MIC ≥ 2 µg/mL, growth on VAN-3 agar, or Etest macromethod positive. Following initial screening, VAN population analysis profiling (PAP) analyses confirmed that 38 patients were infected with hVISA (32).

4.5.3.2 Susceptibilities of Baseline Pathogens

The susceptibility of Gram-positive baseline respiratory pathogens isolated from patients in the MAT population to telavancin and vancomycin (Table 9) was consistent with data from both recent and previously reported surveillance studies for these drugs. The telavancin MIC_{90} against *S. aureus* was 0.5 µg/mL, and the vancomycin MIC_{90} was 1 µg/mL, for both MRSA and MSSA.

The susceptibility of pathogens isolated from patients in the MAT population and recovered from baseline blood cultures was consistent with the data from isolates recovered from respiratory cultures.

Table 9: Susceptibility of Gram-Positive Baseline Respiratory Pathogens to Telavancin and Vancomycin – MAT Population, Studies 0015 and 0019

	MIC (µg/mL)							
	TLV				VAN			
	N	MIC_{50}	MIC_{90}	Range	N	MIC_{50}	MIC_{90}	Range
Organisms From Telavancin-treated Patients								
S. aureus	335	0.25	0.5	0.12−1	335	1	1	≤ 0.25−2
- MRSA	203	0.5	0.5	0.12−1	203	1	1	≤ 0.25−2
- MSSA	132	0.25	0.5	0.12−1	132	1	1	≤ 0.25−2
S. pneumoniae	24	0.015	0.03	0.008−0.03	24	0.25	0.5	0.12−0.5
Organisms from Vancomycin-treated Patients								
S. aureus	312	0.25	0.5	0.06−1	312	1	1	≤ 0.25−2
- MRSA	204	0.5	0.5	0.06−1	204	1	1	≤ 0.25−2
- MSSA	108	0.25	0.5	0.12−0.5	108	1	1	≤ 0.25−2
S. pneumoniae	27	0.015	0.03	0.008−0.06	27	0.25	0.5	0.25−0.5

Note: MIC_{90} values are not presented when sample size is less than 10.
MAT = modified all-treated; MIC = minimum inhibitory concentration; TLV = telavancin; VAN = vancomycin; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-sensitive *S. aureus*.

4.5.4 Dose and Duration of Study Medication

Two patients in Study 0019 who were randomized to receive vancomycin received telavancin instead. One of these patients died on Day 3. All other patients received the study medication assigned at randomization. The mean duration of treatment (approximately 9.5 days) was similar between the telavancin and vancomycin groups (Table 10). The majority of patients received 7 to 14 days of study medication.

Approximately 59% of patients completed the course of study medication. Of those who prematurely discontinued, 7% of patients treated with telavancin and 8% of patients treated with vancomycin discontinued due to 'unsatisfactory therapeutic response, did not receive maximum allowable 21 days of treatment'.

A total of 20 patients randomized to vancomycin were switched to an antistaphylococcal penicillin in a blinded manner, as allowed by the protocol if the baseline pathogen was found to be MSSA. Seventeen of the 20 patients had MSSA, 2 patients had streptococci recovered, and 1 patient had negative cultures. Because so few of the patients with MSSA at baseline were switched to a penicillin (17/120, 14%), the results for these patients are not displayed separately, but rather are included in the vancomycin results.

Table 10: Extent of Exposure to Study Medication – AT Population, Studies 0015 and 0019

	0015		0019		Total	
	TLV (N = 372)	VAN (N = 374)	TLV (N = 377)	VAN (N = 380)	TLV (N =749)	VAN (N = 754)
Days on Study Medication						
Mean, SD	9.1, 4.66	9.4, 4.22	9.9, 4.65	10.0, 4.75	9.5, 4.67	9.7, 4.50
Median	8	9	9	9	9	9
Min, Max	1, 23	1, 22	1, 22	1, 23	1, 23	1, 23
n	372	374	377	380	749	754
Distribution of Days on Study Medication						
< 3 Days	23 (6%)	15 (4%)	17 (5%)	17 (4%)	40 (5%)	32 (4%)
3−6 Days	77 (21%)	62 (17%)	52 (14%)	53 (14%)	129 (17%)	115 (15%)
7−10 Days	152 (41%)	172 (46%)	63 (43%)	160 (42%)	315 (42%)	332 (44%)
11−14 Days	79 (21%)	85 (23%)	95 (25%)	97 (26%)	174 (23%)	182 (24%)
15−21 Days	39 (10%)	38 (10%)	48 (13%)	47 (12%)	87 (12%)	85 (11%)
> 21 Days	2(< 1%)	2 (< 1%)	2 (< 1%)	6 (2%)	4 (< 1%)	8 (1%)

AT = all-treated; TLV = telavancin; VAN = vancomycin; SD = standard deviation; Min = minimum; Max = maximum.

4.5.4.1 Dosage Adjustment Based on Creatinine Clearance

4.5.4.1.1 Telavancin Dosage Adjustment

The dosage of telavancin was 10 mg/kg IV q 24 hours in patients with normal renal function and patients with mild renal insufficiency and was adjusted in patients with moderate to severe renal insufficiency as described in Sections 4.3.5.4 and 4.4.1. The telavancin dosage was selected based on several factors, including a PK-PD assessment that used data from in vitro susceptibility testing, experimental models of infection, and human PK to generate probability estimates for attainment of target AUC that suggested that doses of 750 mg (approximately 10 mg/kg) would result in > 95% probability of AUC target attainment for organisms with MICs as high as 2 µg/mL. The telavancin dosage adjustment in patients

with moderate or severe renal impairment was based on PK considerations and was designed to maintain telavancin exposures at levels comparable to patients with no renal impairment.

The dosing recommendations (10 mg/kg every 24 hours for CrCL > 50 mL/min [normal renal function or mild renal impairment], 7.5 mg/kg every 24 hours for CrCL 30−50 mL/min [moderate renal impairment], and 10 mg/kg every 48 hours for CrCL < 30 mL/min [severe renal impairment]) were followed in NP Studies 0015 and 0019 and patient exposures are shown in Table 11. The mean (± SD) AUC_{0-24} values in patients from Study 0015 and Study 0019 (706 ± 243.6 and 764 ± 280.3 µg•hr/mL, respectively) were comparable to that in healthy subjects (780 ± 125 µg•hr/mL), allowing for the limited number of samples collected in patients and the estimation of AUC values based on them. In Study 0015 and Study 0019, patients who had mild impairment to normal renal function, moderately impaired renal function, and severely impaired renal function had AUC_{0-24} values that were all in the same range (Table 11).

Table 11: Telavancin AUC (0 to 24 Hours) by Baseline CrCL Category – AT Population, Studies 0015 and 0019

		Study 0015 µg•hr/mL (N = 97)	**Study 0019 µg•hr/mL (N = 92)**	**Total µg•hr/mL (N = 189)**
CrCL Category (mL/min)				
> 50 mL/min[a]	Mean ± SD	701 ± 235.3	770 ± 289.7	738 ± 267.0
30−50 mL/min	Mean ± SD	678 ± 274.7	709 ± 224.8	690 ± 252.9
< 30 mL/min	Mean ± SD	783 ± 236.0	835 ± 308.1	798 ± 250.2
Overall	Mean ± SD	706 ± 243.6	764 ± 280.3	734 ± 263.1

Note: CrCL was from a central laboratory.

AUC = area under the concentration-time curve; CrCL = creatinine clearance; AT = all-treated; SD = standard deviation.

[a] Combined CrCL > 80 mL/min and >50−80 mL/min.

Output file: ISE_t_auc_crcl_at_01.rtf

Nearly 90% (667/749) of telavancin patients in the AT population received the protocol-recommended dose according to baseline CrCL. Underdosing was found in 24 (3%) patients overall (16 [3%] patients with CrCL > 50 mL/min, 7 [4%] patients with CrCL 30−50 mL/min, and 1 [1%] patient with CrCL < 30 mL/min), whereas excessive dosing was found in 58 (8%) patients overall (20 [4%] patients with CrCL > 50 mL/min, 31 [19%] patients with CrCL 30−50 mL/min, and 7 [8%] patients with CrCL < 30 mL/min).

4.5.4.1.2 Vancomycin Dosage Adjustment

Table 12 summarizes the initial vancomycin dosage regimens by CrCL at baseline based on local laboratory data for the AT population. The protocol specified a dosage of 1 g IV every 12 hours, which could have been adjusted according to site-specific guidelines based upon patient weight, renal function, or vancomycin serum level monitoring. Given that the

protocol allowed site-specific dosing, the adequacy of vancomycin dosing was determined by comparing the administered doses to the FDA-approved vancomycin product label.

In Table 12, the initial vancomycin dose was examined in terms of mg/kg/day, according to the baseline CrCL as calculated by the investigator for the AT population. In patients with normal renal function, vancomycin was administered at product label-recommended doses in 150 of 287 (52%) patients, at higher than recommended doses in 110 (38%) patients, and at lower than recommended doses in 27 (9%) patients. For patients with some renal impairment, vancomycin was administered at product label-recommended doses in 74 of 465 (16%) patients, at higher than recommended doses in 383 (82%) patients, and at lower than recommended doses in 8 (2%) patients. These data support the adequacy of dosing of vancomycin in the studies.

Table 12: Initial Vancomycin Dosage by Baseline CrCL – AT Population, Studies 0015 and 0019

CrCL[a] (mL/min)	Patients Treated with VAN N (%) (N = 752)	Initial VAN Dose (mg/kg/24hr)	Initial VAN Dose[b] N (%)
> 80 mL/min	287 (38%)	> 30[c]	110 (38%)
		20 to 30[d]	150 (52%)
		< 20[e]	27 (9%)
> 50−80 mL/min	206 (27%)	> 20[c]	166 (81%)
		10 to 20[d]	39 (19%)
		< 10[e]	1 (< 1%)
30−50 mL/min	159 (21%)	> 10[c]	132 (83%)
		6.5 to 10[d]	21 (13%)
		< 6.5[e]	6 (4%)
10−< 30 mL/min	92 (12%)	> 6.5[c]	77 (84%)
		2 to 6.5[d]	14 (15%)
		< 2[e]	1 (1%)
< 10 mL/min	8 (1%)	≥ 2[c]	8 (100%)
		< 2[d]	0

AT = all-treated; CrCL = creatinine clearance; VAN = vancomycin.
[a] Calculated based on actual urine and serum creatinine values or estimated using local laboratory creatinine values.
[b] Calculated as % of patients treated with vancomycin with specified baseline CrCL.
[c] Higher than vancomycin label-recommended dose.
[d] Vancomycin label-recommended dose.
[e] Lower than vancomycin label-recommended dose.

4.5.4.2 Adequacy of Gram-Negative Medications

Adequacy of Gram-negative therapy (defined in Section 4.4.5) is summarized for the AT population in Table 13. Of those patients with mixed infections due to Gram-positive and Gram-negative pathogens, a total of 161 patients (90 of 144 [63%] telavancin and

71 of 126 [56%] vancomycin) did not receive adequate Gram-negative therapy. Overall, a greater proportion of patients in the telavancin group than in the vancomycin group did not receive adequate Gram-negative therapy.

Table 13: Adequacy of Gram-Negative Therapy in Patients with Mixed Gram-Positive / Gram-Negative Infections – AT Population, Studies 0015 and 0019

	Number of Patients					
	0015		0019		Total	
	TLV (N = 50)	VAN (N = 45)	TLV (N = 94)	VAN (N = 81)	TLV (N = 144)	VAN (N = 126)
Mixed Gram-Positive and Gram-Negative Pathogens[a]						
Adequate Gram-Negative Therapy	21 (42%)	22 (49%)	33 (35%)	33 (41%)	54 (38%)	55 (44%)
Inadequate Gram-Negative Therapy	29 (58%)	23 (51%)	61 (65%)	48 (59%)	90 (63%)	71 (56%)
Initial Inadequate Therapy	9 (18%)	5 (11%)	9 (10%)	15 (19%)	18 (13%)	20 (16%)
Never Received Adequate Therapy	20 (40%)	18 (40%)	52 (55%)	33 (41%)	72 (50%)	51 (40%)

AT = all-treated; TLV = telavancin; VAN = vancomycin.
[a] Percentages were calculated based on the total number of patients with Mixed Gram-positive and Gram-negative pathogens.

4.5.5 Clinical Response at Test of Cure – The Protocol-Defined Primary Efficacy Variable

4.5.5.1 Prospectively Planned Analyses of Clinical Response at Test of Cure

- *Clinical cure rates demonstrated noninferiority in the AT and CE analysis groups at the 10% level in both Study 0015 and Study 0019.*

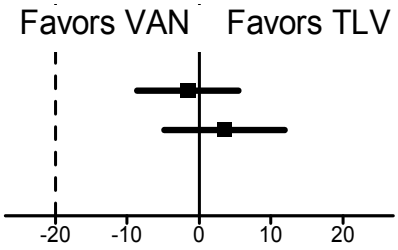
Figure 1 displays the difference (telavancin – vancomycin) in cure rates between telavancin and vancomycin for the AT and CE populations in these studies.

The results of Studies 0015 and 0019 were consistent and demonstrated the noninferiority of telavancin to vancomycin in patients with NP, as evidenced by the lower bound of the 95% CI around the difference (telavancin – vancomycin) in cure rates being greater than the prospectively defined -20% noninferiority margin for both coprimary analysis populations in both studies. For both the AT and CE populations in both studies, the lower bound of the 95% CI around the difference between treatments in cure rates exceeded -10%, and for the aggregate results of Studies 0015 and 0019 in the AT and CE populations, the lower bound of the 95% CI exceeded -6%. The point estimates of the treatment difference (telavancin - vancomycin) in cure rates were consistently positive in the CE population. These data demonstrate that telavancin is effective in the treatment of NP.

Figure 7: Clinical Cure Rates at TOC – AT and CE Populations, Studies 0015 and 0019

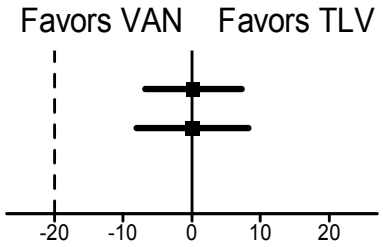
Study 0015

	N	TLV %	VAN %	Delta	95% CI [a]
AT	746	57.5	59.1	-1.6	[-8.6, 5.5]
CE	313	83.7	80.2	3.5	[-5.1, 12]



Study 0019

	N	TLV %	VAN %	Delta	95% CI [a]
AT	757	60.2	60.0	0.2	[-6.8, 7.2]
CE	341	81.3	81.2	0.1	[-8.2, 8.4]



[a] Difference in cure rates (telavancin – vancomycin); 2-sided 95% CI on the difference. Aggregate analysis was stratified by study.
AT = all-treated; CE = clinically evaluable; TLV = telavancin; VAN = vancomycin; TOC = test of cure; CI = confidence interval.

The results of clinical response at TOC in the MAT and ME populations, as well as the results of clinical response at EOT in the AT and CE populations, are consistent with the results of clinical response at TOC.

4.5.5.2 Post-Hoc Sensitivity Analysis by ATS/IDSA Criteria

- *Noninferiority was also demonstrated in the AT-ATS/IDSA group at the 10% level for the AT and CE populations for both Studies 0015 and 0019.*

A sensitivity analysis was conducted after applying the ATS/IDSA diagnostic criteria for NP to the AT population (Section 4.5.9.2.1). They include the presence of a new or progressive radiographic infiltrate plus at least two of three clinical features (fever greater than 38°C, leukocytosis or leukopenia, and purulent secretions). These criteria are proposed herein to identify the patient population in which the post-hoc all-cause mortality endpoint is appropriately assessed. These criteria were met for 634 of 749 patients (85%) in the telavancin group and 655 of 754 patients (87%) in the vancomycin group. All but approximately 1% of patients in each treatment group met the criteria of having chest radiograph findings plus at least one clinical feature. The baseline characteristics of the two treatment groups in this revised patient population were similar, with no important differences noted. Additionally, the characteristics of this population, representing approximately 86% of the overall enrolled and treated population, were similar to the overall population.

The proportions of patients who met the ATS/IDSA criteria and who were deemed clinically evaluable were similar to those of the entire enrolled and treated population. Clinical response at TOC for the analysis populations who met the ATS/IDSA criteria is displayed in Table 14. In both studies and in the aggregate population, noninferiority of telavancin was demonstrated with the lower bound of the 95% CIs of the treatment difference exceeding the prespecified margin of −20%. In fact, the lower bound of the 95% CI exceeded −10% in all populations in both studies, demonstrating the robustness of the findings. As with the AT and CE populations noted above, there were fewer failures among the patients treated with telavancin.

Table 14: Clinical Response (Cure) at TOC – Patients Meeting ATS/IDSA Criteria – AT and CE Populations, Studies 0015 and 0019

	Number of Patients					
	0015		0019		Total	
	TLV	VAN	TLV	VAN	TLV	VAN
AT						
Cure	182/309 (58.9%)	184/316 (58.2%)	194/325 (59.7%)	202/339 (59.6%)	376/634 (59.3%)	386/655 (58.9%)
Difference (95% CI)[a]	0.7% (-7.1%, 8.4%)		0.1% (-7.4%, 7.6%)		0.4% (-5.0%, 5.8%)	
CE						
Cure	99/116 (85.3%)	117/148 (79.1%)	119/147 (81.0%)	121/149 (81.2%)	218/263 (82.9%)	238/297 (80.1%)
Difference (95% CI)[a]	6.3% (-2.9%, 15.5%)		-0.3% (-9.2%, 8.7%)		2.8% (-3.6%, 9.2%)	

[a] Point estimate and 95% CI on the difference in cure rates (telavancin - vancomycin). Aggregate analysis was stratified by study.
AT = all-treated; ATS = American Thoracic Society; IDSA = Infectious Disease Society of America; CE = clinically evaluable; TOC = test of cure; CI = confidence interval; TLV = telavancin; VAN = vancomycin.

4.5.5.3 Clinical Response at Test of Cure by Baseline Pathogen

4.5.5.3.1 Clinical Response at Test of Cure by Baseline Gram-Positive Pathogen

- *Cure rates for patients with S. aureus and specifically MRSA were similar in the two treatment groups in the aggregated data for Studies 0015 and 0019.*
- *In patients infected only with S. aureus, the cure rate was higher in the telavancin group (84.2%) compared with vancomycin (74.3%), difference 9.9% (95% CI: 0.8%, 19.0%).*

In Studies 0015 and 0019, the most common pathogen isolated at baseline was *S. aureus*, which was further categorized as being either MRSA or MSSA. In the aggregate results of Studies 0015 and 0019 in the ME population, the cure rates for patients with *S. aureus*, and specifically MRSA, were similar in the two treatment groups. For patients with MSSA, cure

rates were numerically higher in the telavancin group compared with the vancomycin group in Studies 0015 and 0019, individually and in the aggregate (Table 15).

Other than *S. aureus*, the only Gram-positive pathogen present at baseline in more than 10 patients in either group in the ME population was *S. pneumoniae*; the cure rates for patients with this pathogen were similar between the two treatment groups.

These data indicate that telavancin is effective in treating NP caused by susceptible strains of Gram-positive organisms, including *S. aureus* (including methicillin-resistant and methicillin-susceptible strains) and *S. pneumoniae*.

Table 15: Clinical Cure Rates at TOC by Baseline Gram-Positive Pathogens – ME Population, Studies 0015 and 0019

	Cure Rate[a]					
	0015		0019		Total	
	TLV	VAN	TLV	VAN	TLV	VAN
Gram-Positive Pathogens at Baseline						
S. aureus	80 / 98 (81.6%)	81 / 109 (74.3%)	91 / 121 (75.2%)	80 / 105 (76.2%)	171 / 219 (78.1%)	161 / 214 (75.2%)
- MRSA	57 / 70 (81.4%)	63 / 84 (75.0%)	47 / 69 (68.1%)	52 / 70 (74.3%)	104 / 139 (74.8%)	115 / 154 (74.7%)
- MSSA	26 / 32 (81.3%)	18 / 25 (72.0%)	44 / 52 (84.6%)	29 / 37 (78.4%)	70 / 84 (83.3%)	47 / 62 (75.8%)
S. pneumoniae	9 / 10 (90.0%)	3 / 4 (75.0%)	9 / 10 (90.0%)	15 / 17 (88.2%)	18 / 20 (90.0%)	18 / 21 (85.7%)

ME = microbiologically evaluable; TOC = test of cure; TLV = telavancin; VAN = vancomycin; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-sensitive *S. aureus*.
[a] Cure rate is calculated as the number of patients with the given pathogen and a clinical response of 'cure' divided by the number of patients with the given pathogen.

For patients in the ME population who had a single Gram-positive pathogen and no Gram-negative pathogens isolated at baseline, cure rates in the individual studies consistently were numerically higher in the telavancin group compared with the vancomycin group (Table 16). For the aggregate results of Studies 0015 and 0019, the cure rate at TOC for the telavancin patients who had a single Gram-positive pathogen isolated at baseline was higher than the corresponding cure rate for the vancomycin patients (84.8% vs 75.8%). The point estimate of the treatment difference (telavancin – vancomycin) was 8.9%, and the lower bound of the 95% CI was greater than 0 (0.3%, 17.5%). Similarly, in patients infected only with *S. aureus*, the cure rate was higher in the telavancin group (84.2%) compared with vancomycin (74.3%), difference 9.9% (95% CI: 0.8%, 19.0%).

In patients infected only with MRSA or only with MSSA, cure rates were higher in the telavancin group compared with the vancomycin group in Studies 0015 and 0019, individually and in the aggregate, but the 95% CIs around the treatment difference

(telavancin minus vancomycin) in cure rates included 0, as the smaller numbers of patients in each group widened the CIs for the difference.

There were relatively few patients with *S. pneumoniae* as the sole infecting pathogen. For the aggregate results of the two studies, the cure rates in these patients exceeded 90% in both treatment groups. Similar trends were observed for the MAT population.

Table 16: Clinical Cure Rates at TOC in Patients with Monomicrobial Gram-Positive Infections – ME Population, Studies 0015 and 0019

	Cure Rate[a]					
	0015		0019		Total	
	TLV	VAN	TLV	VAN	TLV	VAN
Monomicrobial Gram-Positive Pathogen						
Gram-Positive Pathogen	68 / 82 (82.9%)	66 / 88 (75.0%)	71 / 82 (86.6%)	59 / 77 (76.6%)	139 / 164 (84.8%)	125 / 165 (75.8%)
				Difference (95% CI)[b]	**9.0% (0.5%, 17.5%)**	
S. aureus	62 / 74 (83.8%)	65 / 87 (74.7%)	61 / 72 (84.7%)	48 / 65 (73.8%)	123 / 146 (84.2%)	113 / 152 (74.3%)
				Difference (95% CI)[b]	**9.9 (0.8%, 19.0%)**	
MRSA	42 / 50 (84.0%)	54 / 70 (77.1%)	30 / 38 (78.9%)	32 / 46 (69.6%)	72 / 88 (81.8%)	86 / 116 (74.1%)
				Difference (95% CI)[b]	**7.7% (-3.7%, 19.0%)**	
MSSA	20 / 24 (83.3%)	11 / 17 (64.7%)	31 / 34 (91.2%)	16 / 19 (84.2%)	51 / 58 (87.9%)	27 / 36 (75.0%)
				Difference (95% CI)[b]	**12.9% (-3.5%, 29.4%)**	
S. pneumoniae	6 / 7 (85.7%)	0 / 0	7 / 7 (100.0%)	11 / 12 (91.7%)	13 / 14 (92.9%)	11 / 12 (91.7%)
				Difference (95% CI)[b]*	**1.2% (-22.7%, 26.3%)**	

TOC = test of cure; ME = microbiologically evaluable; TLV = telavancin; VAN = vancomycin; CI = confidence interval; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-sensitive *S. aureus*.

[a] Cure rate was calculated as the number of patients with given pathogen and a clinical response of 'cure' divided by the number of patients with the given pathogen.

[b] Difference in cure rates = (telavancin – vancomycin); 2-sided 95% CI.

Among the patients with hVISA as their sole baseline pathogen in the MAT population, the cure rates were higher in the telavancin group (5/7, 71% vs. 3/8, 38%), but the numbers were small. Notably, 5 of the 8 vancomycin patients died compared with no deaths in the telavancin group.

4.5.5.3.2 Clinical Response at Test of Cure in Patients with Mixed Baseline Pathogens

- *A subgroup analysis of patients who had mixed Gram-positive and Gram-negative infections showed a lower cure rate for the telavancin group compared with the vancomycin group. More telavancin patients received inadequate Gram-negative antibiotic coverage compared with vancomycin patients. Appropriate antibiotic therapy is necessary for good patient outcomes.*

In patients with mixed Gram-positive and Gram-negative pathogens at baseline (n = 269), both in the aggregate results of Studies 0015 and 0019 and in the individual studies, cure

rates were ~13% lower in the telavancin group (66.2%) than in the vancomycin group (79.4%). Results in the MAT population were similar to those observed in the ME population.

The use of concomitant Gram-negative therapy was left to the investigators' discretion, and a higher proportion of patients in the telavancin group compared with vancomycin group received inadequate Gram-negative antibiotic therapy for some period of time during the study (Table 13). To further explore the reasons for the lower cure rate in the telavancin group, a summary of the baseline characteristics, the adequacy of Gram-negative therapy (as described in Section 4.4.5) and postbaseline cultures in the patients with mixed infections who failed treatment is displayed in Table 17.

There were more telavancin patients compared with vancomycin who received inadequate Gram-negative coverage (defined in Section 4.4.5), who were prior treatment failures (as designated by the investigator after having received at least 3 days prior therapy) (52% vs none), or who were infected with *P. aeruginosa* or *Acinetobacter* spp (83% vs 38%).

Although the number of patients with postbaseline cultures was limited, the data suggest a contribution of Gram-negative pathogens to the failure rate for patients who did not respond to treatment. More telavancin patients had a baseline Gram-negative pathogen that was not eradicated at the postbaseline culture and more potential Gram-negative superinfections, defined as a new postbaseline-identified pathogen when a patient's clinical response was failure at TOC, were observed in the telavancin group. If patients with Gram-negative superinfections are excluded from the analysis, the cure rates are 88.2% and 84.7%, respectively, for the telavancin and vancomycin CE groups.

In vitro and in vivo studies showed no antagonistic interactions or adverse drug:drug PK interactions between telavancin and antibiotics used for Gram-negative infection as summarized in Section 4.2.4.2 and Section 4.3.7.2,. Thus, the higher rate of failure in telavancin patients with mixed infections appears to be a failure to eradicate Gram-negative infection or prevent Gram-negative superinfection in these patients, rather than to a failure of the study medication to eradicate the Gram-positive pathogen isolated at baseline or any impact of telavancin on the efficacy as the antibiotic used for Gram-negative coverage.

Table 17: Characteristics of Patients with Baseline Mixed Infections Who Were Assessed as Failure at TOC – ME Population, Studies 0015 and 0019

	TLV (N=23)	VAN (N=13)
	n (%)	n (%)
Prior Treatment Failure	12 (52%)	0
Pseudomonas aeruginosa or *Acinetobacter* sp.	19 (83%)	5 (38%)
Inadequate Gram-negative Coverage[a]	16 (70%)	6 (46%)
Baseline Gram-positive Eradicated[b]	14 (61%)	4 (31%)
Baseline Gram-negative Eradicated[b]	9 (39%)	6 (46%)
Gram-negative Superinfections[c]	2 (9%)	4 (31%)

TOC = test of cure; ME = microbiologically evaluable; TLV = telavancin; VAN = vancomycin.
[a] Inadequate initial therapy was defined as no or inactive therapy initially and then adequate therapy started at some point during the study evaluation period.
[b] Eradication was defined as failing to identify the baseline pathogen in the last postbaseline culture. At least one postbaseline culture was required for eradication.
[c] Superinfection was defined as identification of a pathogen in a postbaseline culture that was not present in a baseline culture in patients who were failure at TOC.

4.5.5.3.3 Clinical Response by Baseline Pathogen Susceptibility (MIC)

- *For single pathogen infections due to S. aureus, including MRSA and MSSA, with vancomycin susceptibilities ≥ 1.0 µg/mL, cure rates were significantly higher in the telavancin group compared with the vancomycin group.*

In telavancin patients with *S. aureus* at baseline (patients with a single pathogen only), clinical cure rates (summarized according to the in vitro susceptibility of the pathogen to telavancin in Table 18) were consistent across the range of MICs for MRSA and MSSA in the ME populations. Similar results were observed for the MAT population.

Table 18: Clinical Response at TOC in Telavancin Patients According to In Vitro Susceptibility to Telavancin of *S. aureus* Recovered at Baseline – ME Population, Aggregated Studies 0015 and 0019

	MIC (µg/mL) of TLV			
	0.12	0.25	0.5	1.0
MRSA	1 / 1 (100.0%)	27 / 33 (81.8%)	30 / 33 (90.9%)	3 / 3 (100.0%)
MSSA	2 / 2 (100.0%)	34 / 39 (87.2%)	10 / 11 (90.9%)	0 / 0

Note: Cells show the number of patients with clinical cure divided by the number of patients with the given pathogen.
Note: Only includes patients with single baseline pathogen.
TOC = test of cure; ME = microbiologically evaluable; MIC = minimum inhibitory concentration; TLV = telavancin; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-sensitive *S. aureus.*

Table 19 summarizes cure rates of patients with *S. aureus* isolated at baseline as the only pathogen, according to the in vitro susceptibility of the *S. aureus* to vancomycin. For single pathogen infections due to *S. aureus*, including MRSA and MSSA, with vancomycin susceptibilities ≤ 0.5 µg/mL as well as ≥ 1.0 µg/mL, cure rates were significantly higher in the telavancin group compared with the vancomycin group. The difference between the telavancin and vancomycin cure rates for all *S. aureus* with vancomycin MIC ≥ 1.0 µg/mL was 12.8% (87.1% vs 74.3%) with the 95% CI for the difference of 1.8% to 23.8%.

Table 19: Clinical Response at TOC According to In Vitro Susceptibility to Vancomycin of *S. aureus* Recovered at Baseline – ME Population, Aggregated Studies 0015 and 0019

	VAN MIC (µg/mL) ≤ 0.5[a]		**VAN MIC (µg/mL) ≥ 1.0[b]**	
	TLV	**VAN**	**TLV**	**VAN**
S. aureus	33 / 37 (89.2%)	22 / 28 (78.6%)	74 / 85 (87.1%)	78 / 105 (74.3%)
MRSA	11 / 12 (91.7%)	12 / 14 (85.7%)	50 / 58 (86.2%)	66 / 88 (75.0%)
MSSA	22 / 25 (88.0%)	10 / 14 (71.4%)	24 / 27 (88.9%)	12 / 17 (70.6%)

Note: Cells show the number of patients with clinical cure divided by the number of patients with the given pathogen.
Note: Only includes patients with single baseline pathogen.
TOC = test of cure; ME = microbiologically evaluable; MIC = minimum inhibitory concentration; TLV = telavancin; VAN = vancomycin; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-sensitive *S. aureus*.
[a] All MICs are 0.5 ug/mL, except for one telavancin patient with MIC ≤ 0.25 ug/mL.
[b] All MICs are 1.0 ug/mL, except for two telavancin patients with MIC = 2.0 ug/mL.

4.5.6 Microbiologic Response

Microbiologic response data (eradication of pathogens) are not presented since relatively small numbers of patients (per protocol) had postbaseline cultures obtained. Investigators were instructed to perform postbaseline cultures if clinically indicated, hence, they generally only were performed in those patients who were not doing well clinically. As a result, the microbiologic response rates were very similar to the clinical response rates, since, in the absence of culture data, the microbiologic response was driven by the clinical response (eg, cured implied eradicated in the absence of a culture, and failure implied persisted). Postbaseline culture data are explored in the context of clinical failures in patients with mixed infections in Section 4.5.5.3.2.

4.5.7 Development of Resistance or Decreased Susceptibility

Breakpoints for telavancin have not been set, so development of resistance cannot be defined. Therefore, reduced susceptibility was defined as a 4-fold increase from baseline MIC to a postbaseline value. No organisms recovered from a postbaseline culture had more than a 2-fold increase in telavancin or vancomycin MIC.

4.5.8 Results in Subpopulations

4.5.8.1 Subgroups at High Risk

Results are also presented for the following prospectively defined subgroups in the CE population, selected to represent groups of patients with more serious illness or those at greater risk for poor outcomes: bacteremic pneumonia (defined as having the same pathogen in baseline blood and respiratory cultures), APACHE II score ≥ 20, and age ≥ 65 years. In each of these subgroups, the telavancin cure rates were numerically higher than in the patients who were treated with vancomycin (Table 20). Among the patients with bacteremic pneumonia, there were 6 vancomycin patients and only 2 telavancin patients with persistent bacteremia (positive blood cultures up to Day 7).

Table 20: Cure Rates in Subgroups at High Risk – CE Population, Aggregated Studies 0015 and 0019

		Cure Rate		
	n	TLV	VAN	Difference (95% CI)[a]
Bacteremia	29	86.7%	78.6%	8.1% (-20.5, 35.3)
APACHE II ≥ 20	117	69.6%	59.0%	10.6% (-6.6, 27.9)
Age ≥ 65 Years	347	80.6%	76.0%	4.6% (-4.1, 13.3)

CE = clinically evaluable; TLV = telavancin; VAN = vancomycin; CI = confidence interval; APACHE = Acute Physiology and Chronic Health Evaluation.
[a] Difference in cure rates (telavancin – vancomycin); 2-sided 95% CI stratified by study.

4.5.8.2 Analysis of Response in the Subgroup of Patients with Ventilator-Associated Pneumonia

Because patients with VAP constitute one of the most severely ill subpopulations among those with NP, efficacy results in this cohort were explored. Accordingly, as prospectively defined, patients were categorized as either having VAP or non–ventilator-associated nosocomial pneumonia (NVANP). If the interval between intubation and NP diagnosis was greater than 2 days, the patient was categorized as having VAP.

Of the 1503 patients in the AT population, 427 patients (216 telavancin patients and 211 vancomycin patients) were categorized as having VAP and 1076 patients (533 telavancin patients and 543 vancomycin patients) were categorized as having NVANP. Table 21 summarizes the number and percentage of patients in each of the efficacy analysis populations in VAP. For patients with VAP, 91% of telavancin patients and 83% of vancomycin patients in CE population also met the criteria for inclusion in the ME population (ie, had a Gram-positive baseline pathogen).

Table 21: Analysis Populations Based on Diagnosis of VAP – Studies 0015 and 0019

	Number of Patients					
	0015		0019		Total	
	TLV (N = 103)	VAN (N = 100)	TLV (N = 113)	VAN (N = 111)	TLV (N = 216)	VAN (N = 211)
AT	103 (100%)	100 (100%)	113 (100%)	111 (100%)	216 (100%)	211 (100%)
MAT	83 (81%)	73 (73%)	101 (89%)	88 (79%)	84 (85%)	161 (76%)
Respiratory Pathogens	83 (100%)	72 (99%)	100 (99%)	88 (100%)	183 (99%)	160 (99%)
Blood Pathogens Only	0	1 (1%)	1 (< 1%)	0	1 (< 1%)	1 (< 1%)
CE	29 (28%)	33 (33%)	41 (36%)	32 (29%)	70 (32%)	65 (31%)
ME	26 (25%)	26 (26%)	38 (34%)	28 (25%)	64 (30%)	54 (26%)
Respiratory Pathogens	26 (100%)	26 (100%)	38 (100%)	28 (100%)	64 (100%)	54 (100%)
ME as % of CE Population	90%	79%	93%	88%	91%	83%

Note: MAT, CE, and ME percentages were calculated relative to the number in the AT population.
VAP = ventilator-associated pneumonia; TLV = telavancin; VAN = vancomycin; AT = all-treated; MAT = modified all-treated; CE = clinically evaluable; ME = microbiologically evaluable.

Baseline characteristics were similar between treatment groups for patients with VAP and for patients with NVANP. However, in the CE population only in Study 0015, there were more VAP patients < 65 years old in the telavancin treatment group.

For VAP patients in the AT and CE populations, APACHE scores were similar between the two treatment groups overall (mean and median scores approximately 17 to 18). Patients were intubated for 8 or more days before diagnosis of VAP in 38 of 70 (54.3%) of telavancin patients compared with 27 of 65 (41.5%) of vancomycin patients. There were no notable differences across treatment groups in the proportion who were diabetic or in the distribution of Clinical Pulmonary Infection Scores (CPIS) (mean and median scores of 8).

All patients with VAP in the ME population had to have a Gram-positive pathogen recovered from baseline cultures.

S. aureus was the most frequently isolated pathogen at baseline across treatment groups in both populations, with the majority (~60%) of the isolates being MRSA in the ME population. *P. aeruginosa* and *Acinetobacter* spp. were the most common Gram-negative pathogens.

There were relatively few patients with VAP in the ME population with pathogens recovered from blood cultures at baseline. In the ME population of the aggregate study results, 7 telavancin patients had Gram-positive blood pathogens from baseline cultures compared with 1 vancomycin patient.

Clinical Response at Test of Cure in Patients with Ventilator-Associated Pneumonia

In Table 22, clinical response at TOC is summarized for patients with VAP in the ME population who received telavancin or vancomycin in Study 0015 and Study 0019, both individually and in the aggregate. In the aggregate ME population, the cure rate for

telavancin (78%) was significantly greater than that for vancomycin (61%; difference [95% CI]: 17.5% [0.3%, 32.7%]).

Table 22: Clinical Response at TOC in Patients with VAP – ME Population, Studies 0015 and 0019

	Number of Patients					
	0015		0019		Total	
	TLV	VAN	TLV	VAN	TLV	VAN
ME, N	26	26	38	28	64	54
Cure	23 (88.5%)	15 (57.7%)	27 (71.1%)	18 (64.3%)	50 (78.1%)	33 (61.1%)
Difference (95% CI)[a]	30.8% (6.1%, 51.0%)†		6.8% (-16.1%, 29.6%)		17.5% (0.3%, 32.7%)†	

† = CI uses Agresti-Caffo adjustment. Aggregate analysis was stratified by study.
TOC = test of cure; VAP = ventilator-associated pneumonia; ME = microbiologically evaluable; TLV = telavancin; VAN = vancomycin; CI = confidence interval.
[a] Point estimate and 95% CI on the difference in cure rates (telavancin - vancomycin). The analysis was stratified by study.

Clinical Response by Pathogen in Patients with Ventilator-Associated Pneumonia

In Table 23, clinical response at TOC by the most common pathogens is summarized for patients with VAP in the ME population that received telavancin or vancomycin in Study 0015 and Study 0019, both individually and in the aggregate. Among the 118 patients in the ME population with VAP, 109 had *S. aureus* as a baseline pathogen. Cure rates were consistently higher in the telavancin group (76.3%) compared with the vancomycin group (60.0%) for patients with VAP due to *S. aureus.* This also was true both for the subsets of patients with VAP due to MRSA (75.0% vs 57.6%), and VAP due to MSSA (79.2% vs 64.7%). There were far fewer patients with VAP due to *S. pneumoniae*: 4 of 5 telavancin patients were cured compared with 1 of 2 vancomycin patients.

Table 23: Clinical Response at TOC by Baseline Gram-Positive Pathogens in Patients with VAP – ME Population, Studies 0015 and 0019

	Cure Rate[a]					
	0015		0019		Total	
	TLV	VAN	TLV	VAN	TLV	VAN
Gram-Positive Pathogens at Baseline						
S. aureus	20 / 23 (87.0%)	14 / 25 (56.0%)	25 / 36 (69.4%)	16 / 25 (64.0%)	45 / 59 (76.3%)	30 / 50 (60.0%)
- MRSA	15 / 17 (88.2%)	9 / 18 (50.0%)	12 / 19 (63.2%)	10 / 15 (66.7%)	27 / 36 (75.0%)	19 / 33 (57.6%)
- MSSA	6 / 7 (85.7%)	5 / 7 (71.4%)	13 / 17 (76.5%)	6 / 10 (60.0%)	19 / 24 (79.2%)	11 / 17 (64.7%)
S. pneumoniae	3 / 3 (100.0%)	1 / 1 (100.0%)	1 / 2 (50.0%)	0 / 1 (0.0%)	4 / 5 (80.0%)	1 / 2 (50.0%)

TOC = test of cure; VAP = ventilator-associated pneumonia; ME = microbiologically evaluable; TLV = telavancin; VAN = vancomycin; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-sensitive *S. aureus*.
[a] Cure rate was calculated as the number of patients with the given pathogen and a clinical response of 'cure' divided by the number of patients with the given pathogen.

4.5.8.3 Clinical Response by Baseline Renal Function

In the cSSSI studies for telavancin, decreased clinical response rate (cure) was observed in patients with moderate to severe renal impairment (CrCL < 50 mL/min). Table 24 displays the results of clinical response by baseline CrCL category in the AT population in Studies 0015 and 0019. Lower cure rates were observed in both treatment groups among patients with severe renal impairment, but the cure rates in the telavancin group were lower than for vancomycin (by 5% and 9%) in patients with moderate and severe impairment, respectively.

Table 24: Clinical Response by Baseline Renal Function – AT Population, Aggregated Studies 0015 and 0019

		Cure Rate		
CrCL (mL/min)	N	TLV	VAN	Difference TLV – VAN % (95% CI)
< 30	191	38.4%	47.8%	-9.4 (-23.4, 4.6)
30−50	293	54.2%	58.9%	-4.7 (-16.1, 6.6)
50−80	362	59.2%	61.8%	-2.6 (-12.6, 7.5)
>80	657	67.0%	61.9%	5.1 (-2.2, 12.4)

AT = all-treated; CrCL = creatinine clearance; TLV = telavancin; VAN = vancomycin; CI = confidence interval.

4.5.9 Mortality Analysis

4.5.9.1 Rationale for Post-Hoc Assessment of All-Cause Mortality

All-cause mortality was proposed in the 2010 FDA Draft Guidance for clinical trials in NP as the only endpoint that can be scientifically supported if noninferiority design trials are to be performed for the evaluation of antibiotics (FDA Draft Guidance for Industry: Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment; November 2010). The advantages of the mortality endpoint are its objectivity and the historical literature (albeit limited) demonstrating a substantial benefit in mortality reduction by the application of appropriate antibiotics in patients with VAP.

The endpoint is potentially problematic in that seriously ill patients with nosocomial infections, including NP, usually die of underlying conditions, for which they were hospitalized in the first place, or chronic illnesses that are exacerbated by the acute illness (2, 16). Therefore, the endpoint would be expected to be relatively insensitive to the effects of antibiotics on the infection.

The prospective primary analysis for Studies 0015 and 0019 was an evaluation of telavancin's clinical noninferiority to vancomycin, with respect to clinical response at the TOC assessment. Subsequent to the completion of Studies 0015 and 0019 and analysis of these data, Theravance became aware of increased interest in the use of all-cause mortality as an outcome measure (of efficacy) in NP. On the basis of discussions with the Agency and in consideration of the November 2010 FDA Draft Guidance for Industry: "Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment," a data collection effort was undertaken to obtain vital status (survival) information up to 49 days postrandomization in all treated patients.

To optimize the value of this analysis, the clinical research sites were queried to collect available data (eg, alive or dead, date of death, cause of death) for each patient. Updated information was received for 89.3% of the queries (593/664 queries). Thus, vital status at Day 28 was known for approximately 95% of treated patients. For analysis purposes, the patients missing vital status at Day 28 were treated as censored based on the last time of observation. The number of deaths in the aggregated studies was 178 (23.8%) in the telavancin group and 164 (21.8%) in the vancomycin group. The vital status data was summarized at Day 28 in the AT population. A total of 153 new deaths or death updates were obtained, including 11 new deaths and/or updates during Study Day 1 to 28.

4.5.9.2 Analysis of Study 0015, Study 0019, and Aggregate Data

- *The 28-day treatment mortality differences were inconsistent between Study 0019 and Study 0015. In Study 0015, the mortality rate for the telavancin group was 5.8% higher than for the vancomycin group. In Study 0019, the mortality rate for the telavancin group was 1.9% lower than for the vancomycin group.*
- *Exploratory analysis for mortality showed an interaction between CrCL < 30 mL/min and treatment group in favor of vancomycin.*

- *A variety of post-hoc analysis sets were constructed for sensitivity analyses of the effect of different patient characteristics on the mortality differences between treatment groups.*

The primary objective of the post-hoc analyses was to examine the noninferiority, with respect to all-cause mortality, of telavancin to vancomycin in the treatment of patients with NP. In order to refine and enhance the sensitivity of the analysis, the ATS/IDSA criteria for the diagnosis of NP were applied to the AT analysis population (see Section 4.5.9.2.1). Therefore the primary analysis population for the post-hoc mortality analysis was the AT-ATS/IDSA population. The primary endpoint was all-cause mortality evaluated at Day 28. To account for the censored data, Kaplan-Meier survival point estimates at 28 days were calculated with corresponding 2-sided 95% linear CIs of the difference in rates between the two treatments. Noninferiority of telavancin to vancomycin was met when the lower bound of the 95% CI was greater than −0.10.

4.5.9.2.1 Justification for Use of ATS/IDSA Population for Mortality Analyses

The inclusion criteria used in Studies 0015 and 0019 replicated those of a prior registrational trial that led to approval of an antibiotic for NP (49). These criteria were consistent with, but not identical to, available FDA guidance (Draft Guidance for Industry, “Nosocomial Pneumonia — Developing Antimicrobial Drugs for Treatment,” published in 1998).

In 2005, after the initiation of the NP studies, the ATS/IDSA guidance for the diagnosis and management of NP was published (2). The criteria for the clinical diagnosis of pneumonia recommended by the ATS/IDSA are the most sensitive/specific for identification of patients likely to have pneumonia (2). They include the presence of a new or progressive radiographic infiltrate plus at least two of three clinical features (fever greater than 38°C, leukocytosis or leukopenia, and purulent secretions). Collectively, these criteria are considered to represent the most accurate (balance of sensitivity and specificity) combination of clinical findings for starting empiric antibiotic therapy. The latter consideration is important given the relatively low sensitivity of an all-cause mortality endpoint in detecting treatment effects of antibiotics in NP, wherein mortality attributable to the infection under study may be very low (~1 to 2%) (5). These criteria are also included in the 2010 draft guidance from the FDA for developing drugs for HABP/VABP. Applying these criteria to the patients enrolled in Studies 0015 and 0019 resulted in a population that accounts for approximately 86% of the enrolled patients (see Table 25).

Therefore, the ATS/IDSA All-Treated (AT−ATS/IDSA) analysis set is the primary analysis set and includes patients who met all the following:

- Were randomized into the study
- Received at least one dose of study medication
- Met the additional ATS/IDSA pneumonia diagnosis criteria (2) as follows:
  - Evidence of a new or progressive infiltrate on chest radiograph
  - And at least two of the following features:

- Fever > 38°C
- Leukocytosis or leucopenia
- Purulent lower respiratory tract secretions

The AT-ATS/IDSA analysis set is the analysis group for the mortality efficacy hypothesis test.

The primary analysis set (AT-ATS/IDSA) contained a total of 1289 patients (86% of the AT), divided approximately equally between treatment groups, but with a greater proportion in Study 0019 (664 patients) than in Study 0015 (625 patients).

4.5.9.2.2 Post-Hoc Analysis Sets

A summary of post-hoc-defined analysis sets is presented in Table 25. A summary of prespecified analysis sets were presented in Section 4.4.7.2 (Table 4). The ATS/IDSA criteria were applied to patients enrolled in Studies 0015 and 0019, and the AT-ATS/IDSA analysis set was the analysis set for the primary efficacy objective (Section 4.5.9.2.1). The multiple analysis groups were intended to shed light on how different types of patients (strict pneumonia definition, Gram-positive infections only, mixed Gram-positive/Gram-negative infections, MRSA infections) influenced conclusions.

Table 25: Summary of Post-Hoc-Defined Analysis Sets

Abbreviation	Name	Definition	Sample Size
AT−ATS/IDSA	Primary (All-Treated ATS/IDSA)	Patients in the AT analysis set who met ATS/IDSA pneumonia criteria	1289 (85.8%)
MAT-ATS/IDSA	ATS/IDSA Modified All-Treated	Patients in the MAT analysis set who met ATS/IDSA pneumonia criteria	951 (63.3%)
PP	Per Protocol	Patients in the MAT analysis set who had at least one Gram-positive baseline respiratory pathogen	797 (53.0%)
PP-ATS/IDSA	ATS/IDSA Per Protocol	Patients in the PP analysis set who met ATS/IDSA pneumonia criteria	694 (46.2%)
MPP	Modified Per Protocol	Patients in the PP analysis set with only Gram-positive baseline pathogens	527 (35.1%)
MPP-ATS/IDSA	ATS/ISDA Modified Per Protocol	Patients in the MPP analysis set who met ATS/IDSA pneumonia criteria	449 (29.9%)
MRSA	MRSA	Patients in the PP analysis set with at least one MRSA identified at baseline	464 (30.9%)
MRSA-ATS/IDSA	ATS/IDSA MRSA	Patients in the MRSA analysis set who met ATS/IDSA pneumonia criteria	400 (26.6%)
MMRSA	Modified MRSA	Patients in the PP analysis set with only MRSA identified at baseline.	295 (19.6%)
MMRSA-ATS/IDSA	ATS/IDSA Modified MRSA	Patients in the MMRSA analysis set who met ATS/IDSA pneumonia criteria	245 (16.3%)

AT = all-treated; ATS = American Thoracic Society; IDSA = Infectious Disease Society of America; MAT = modified all-treated; PP = per protocol; MPP = modified per protocol; MRSA = methicillin-resistant *S. aureus*; MMRSA = modified methicillin-resistant *S. aureus*.

One disadvantage of a post-hoc analysis is the inability to specify the sample size to be enrolled to provide an adequate degree of statistical power for the hypothesis being examined. In the case of Studies 0015 and 0019, only the number of patients available for each of the post-hoc-defined analyses can be calculated with corresponding post-hoc statistical power.

Table 26 displays the statistical power calculations for specific analysis sets and their modifications. Adequate statistical power (~80% or greater) for the mortality endpoint was found in both studies individually and the aggregated studies for the AT-ATS/IDSA (primary) analysis set. In the microbiologic subsets of interest (PP-ATS/IDSA and MPP-ATS/IDSA), only the aggregated studies have sufficient statistical power to demonstrate noninferiority.

Table 26: Post Hoc Power Calculations for All-Cause Mortality by Study and Aggregated Across Studies

Abbreviation	Study 0015	Study 0019	Studies 0015 and 0019
AT−ATS/IDSA	88%	90%	99%
PP-ATS/IDSA	59%	67%	90%
MPP-ATS/IDSA	47%	45%	75%
MMRSA-ATS/IDSA	32%	24%	50%

AT = all-treated; ATS = American Thoracic Society; IDSA = Infectious Disease Society of America; PP = per protocol; MPP = modified per protocol; MMRSA = modified methicillin-resistant *S. aureus*.

4.5.9.2.3 Background Characteristics

Demographic and baseline characteristics of the AT-ATS/IDSA population are presented in Table 27. Similar frequencies of the various characteristics were observed between the treatment groups across the studies as compared with the AT population (see Section 4.5.2).

Table 27: Demographic and Baseline Characteristics – AT-ATS/IDSA Population, Studies 0015 and 0019

	Number of Patients					
	0015		0019		Total	
	TLV (N = 309)	VAN (N = 316)	TLV (N = 325)	VAN (N = 339)	TLV (N = 634)	VAN (N = 655)
Age (Years)						
Mean ± SD	62 ± 19.1	64 ± 17.1	60 ± 17.8	61 ± 18.1	61 ±1 8.4	62 ± 17.7
≥ 65 Years	160 (52%)	176 (56%)	159 (49%)	167 (49%)	319 (50%)	343 (52%)
≥ 75 Years	101 (33%)	99 (31%)	82 (25%)	92 (27%)	183 (29%)	191 (29%)
Sex (n)						
Female	107 (35%)	139 (44%)	101 (31%)	115 (34%)	208 (33%)	254 (39%)
Race (n)						
White	222 (72%)	232 (73%)	209 (64%)	224 (66%)	431 (68%)	456 (70%)
Black, of African Heritage	8 (3%)	10 (3%)	13 (4%)	5 (1%)	21 (3%)	15 (2%)
Asian	75 (24%)	73 (23%)	72 (22%)	83 (24%)	147 (23%)	156 (24%)
Other (Include Multiple Race)	4 (1%)	1 (<1%)	31 (10%)	27 (8%)	35 (6%)	28 (4%)
Medical History						
Diabetes	92 (30%)	92 (29%)	73 (22%)	61 (18%)	165 (26%)	153 (23%)
Congestive Heart Failure	48 (16%)	66 (21%)	49 (15%)	53 (16%)	97 (15%)	119 (18%)
COPD	63 (20%)	76 (24%)	66 (20%)	70 (21%)	129 (20%)	146 (22%)
Chronic Renal Failure	29 (9%)	30 (9%)	8 (2%)	13 (4%)	37 (6%)	43 (7%)
Shock	13 (4%)	22 (7%)	13 (4%)	14 (4%)	26 (4%)	36 (5%)
ARDS	21 (7%)	18 (6%)	8 (2%)	10 (3%)	29 (5%)	28 (4%)
ALI (but not ARDS)	26 (8%)	18 (6%)	15 (5%)	11 (3%)	41 (6%)	29 (4%)
ICU						
ICU at Baseline	188 (61%)	191 (60%)	177 (54%)	198 (58%)	365 (58%)	389 (59%)
Vasopressors/Inotropics[a]						
Use of Vasopressors/ Inotropics	26 (8%)	41 (13%)	20 (6%)	41 (12%)	46 (7%)	82 (13%)
Baseline Renal Status						
CrCL ≤ 50 mL/min	117 (38%)	124 (39%)	91 (28%)	91 (27%)	208 (33%)	215 (33%)
CrCL < 30 mL/min	50 (16%)	44 (14%)	33 (10%)	39 (12%)	83 (13%)	83 (13%)
Acute Renal Failure	38 (12%)	30 (9%)	26 (8%)	28 (8%)	64 (10%)	58 (9%)
Hemodialysis	9 (3%)	8 (3%)	3 (<1%)	5 (1%)	12 (2%)	13 (2%)
APACHE II[b]						
Mean ± SD	16 ± 6.6	16 ± 6.4	15 ± 6.3	16 ± 6.7	15 ± 6.5	16 ± 6.6

Table 27: Demographic and Baseline Characteristics – AT-ATS/IDSA Population, Studies 0015 and 0019

	Number of Patients					
	0015		0019		Total	
	TLV (N = 309)	VAN (N = 316)	TLV (N = 325)	VAN (N = 339)	TLV (N = 634)	VAN (N = 655)
Type of Pneumonia						
VAP	94 (30%)	88 (28%)	103 (32%)	103 (30%)	197 (31%)	191 (29%)
Late VAP (≥ 4 Days on Ventilation at Diagnosis)	83 (27%)	71 (22%)	91 (28%)	83 (24%)	174 (27%)	154 (24%)
PaO^2/FiO^2 (Mean ± SD)	250 ± 106.5	227 ± 95.1	254 ± 173.6	258 ± 148.5	252 ± 144.9	244 ± 127.2
NVAHAP	215 (70%)	228 (72%)	222 (68%)	236 (70%)	437 (69%)	464 (71%)
Sign of Pneumonia						
Fever (Temp > 38°C)	249 (81%)	242 (77%)	280 (86%)	290 (86%)	529 (83%)	532 (81%)
WBC > 10000/mm³ [c]	210 (75%)	191 (73%)	188 (68%)	202 (69%)	398 (71%)	393 (71%)
Purulent Secretions	295 (95%)	303 (96%)	312 (96%)	335 (99%)	607 (96%)	638 (97%)
Heart Rate > 120/min	68 (22%)	63 (20%)	56 (17%)	59 (17%)	124 (20%)	122 (19%)
Respiratory Rate > 30/min	117 (38%)	118 (37%)	83 (26%)	97 (29%)	200 (32%)	215 (33%)
SIRS[d]	280 (91%)	281 (89%)	284 (87%)	301 (89%)	564 (89%)	582 (89%)
Radiological Characteristics						
Multilobar Involvement	197 (64%)	191 (60%)	206 (63%)	207 (61%)	403 (64%)	398 (61%)
Pleural Effusion	96 (31%)	105 (33%)	86 (26%)	96 (28%)	182 (29%)	201 (31%)
Prior Antibiotic Use (> 24 Hrs Prior to Enrollment)						
Used Prior Antibiotic (> 24 Hrs)	151 (49%)	179 (57%)	179 (55%)	195 (58%)	330 (52%)	374 (57%)
Pathogen Resistant to Prior Antibiotic Therapy[e]	26 (17%)	36 (20%)	45 (25%)	51 (26%)	71 (22%)	87 (23%)
Failed Prior Antibiotic Therapy for NP[e]	74 (49%)	70 (39%)	109 (61%)	111 (57%)	183 (55%)	181 (48%)
Pneumonia Occurred Despite Prior Antibiotics[e]	77 (51%)	93 (52%)	86 (48%)	88 (45%)	163 (49%)	181 (48%)

* Fisher's exact test for character variables; 2-sided Wilcoxon test for continuous variables.

AT = all-treated; ATS = American Thoracic Society; IDSA = Infectious Disease Society of America; TLV = telavancin; VAN = vancomycin; SD = standard deviation; COPD = chronic obstructive pulmonary disease; CrCL = creatinine clearance; ARDS = acute respiratory distress syndrome; ALI = acute lung injury; ICU = intensive care unit; APACHE = Acute Physiology and Chronic Health Evaluation; VAP = ventilator-associated pneumonia; NVAHAP = non–ventilator-associated hospital-acquired pneumonia; WBC = white blood cell; SIRS = Systemic Inflammatory Response Syndrome; NP = nosocomial pneumonia.

[a] Use of dopamine, norepinephrine, dobutamine, epinephrine, or phenylephrine.

[b] Components with missing value were converted to 0.

[c] Denominator included only patients with a baseline WBC result.

[d] SIRS: patients presented with two or more of the following criteria: 1) temperature > 38ºC or < 36ºC, 2) heart rate > 90 beats/minute, 3) respiration > 20/min or $PaCO_2$ < 32 mmHg, 4) leukocyte count > 12000/mm^3 or < 4000/mm^3, or > 10% immature (band) cells.

[e] Denominator based on the number of patients who used > 24 hours prior antibiotic.

4.5.9.2.4 Characteristics of Patients Who Did Not Meet ATS/IDSA Criteria

The patients who did not meet the ATS/IDSA criteria had substantially higher rates of cardiovascular and chronic pulmonary comorbid conditions, such as diabetes mellitus,

congestive heart failure, and chronic obstructive pulmonary disease (COPD) and may have presented symptoms that appeared to investigators to be cases of NP. Substantially fewer patients who did not meet the ATS/IDSA criteria had the typical signs and symptoms of pneumonia (eg, fever, elevated WBC count, and purulent secretions) compared with the patients in the primary and target analysis sets. Additionally, only approximately half the patients who did not meet the ATS/IDSA criteria had evidence of Systemic Inflammatory Response Syndrome (SIRS), compared with nearly 90% of the patients in the primary analysis set.

4.5.9.3 Primary Mortality Analysis in Studies 0015 and 0019

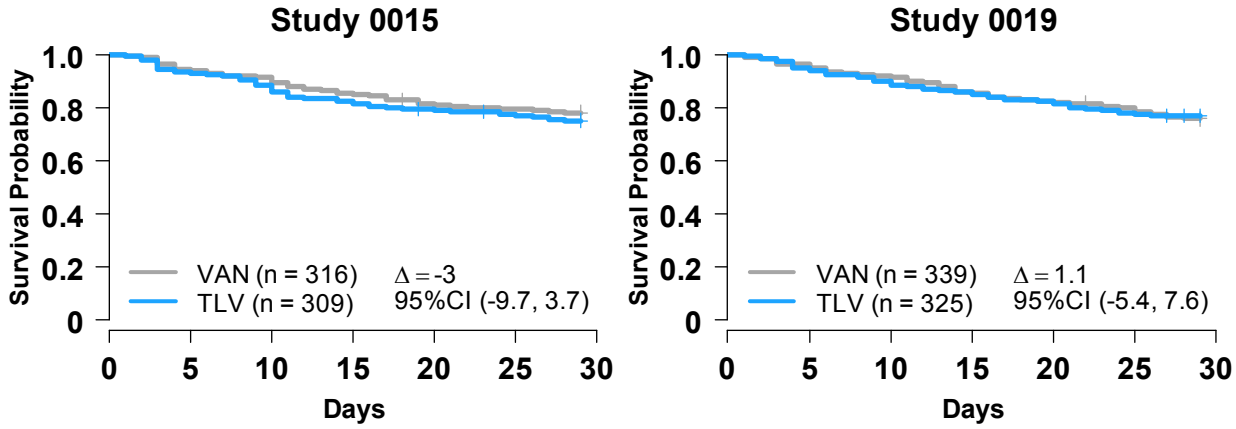
4.5.9.3.1 AT-ATS/IDSA Population

- *Both studies met a 10% noninferiority margin for mortality in the AT-ATSIDSA analysis group.*

Kaplan-Meier survival curves for the AT-ATS/IDSA analysis set for Studies 0015 and 0019 are presented in Figure 8.

For the AT-ATS/IDSA analysis set, noninferiority of telavancin to vancomycin in the treatment of NP was demonstrated for 28-day all-cause mortality in each study (lower limit of 95% CI of treatment difference greater than −10%).

Figure 8: Kaplan-Meier Survival Curves – AT-ATS/IDSA Population, Studies 0015 and 0019



AT = all-treated; ATS = American Thoracic Society; IDSA = Infectious Disease Society of America; VAN = vancomycin; TLV = telavancin; CI = confidence interval.

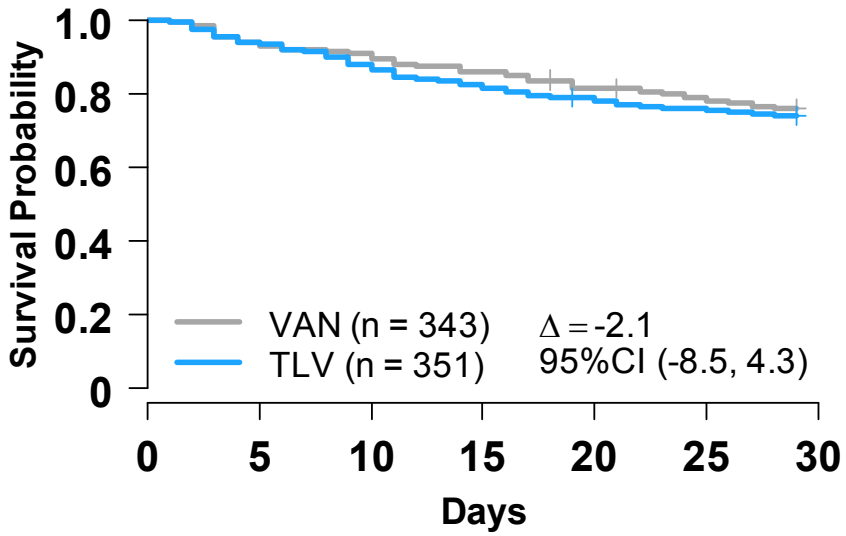
4.5.9.3.2 PP-ATS/IDSA Population

- *The PP-ATS-IDSA analysis group, aggregated across studies, met the 10% noninferiority margin for mortality.*

A Kaplan-Meier survival curve for the PP-ATS/IDSA analysis set (patients with at least a Gram-positive pathogen) for the aggregate of Studies 0015 and 0019 is presented in Figure 9. The aggregated studies achieved 90% power (see Table 26).

For the PP-ATS/IDSA analysis set, noninferiority of telavancin to vancomycin in the treatment of NP was demonstrated for 28-day all-cause mortality in the aggregated studies (lower limit of 95% CI of treatment difference greater than -10%).

Figure 9: Kaplan-Meier Survival Curve – PP-ATS/IDSA Population, Aggregated Studies 0015 and 0019



PP = per protocol; ATS = American Thoracic Society; IDSA = Infectious Disease Society of America; VAN = vancomycin; TLV = telavancin; CI = confidence interval.

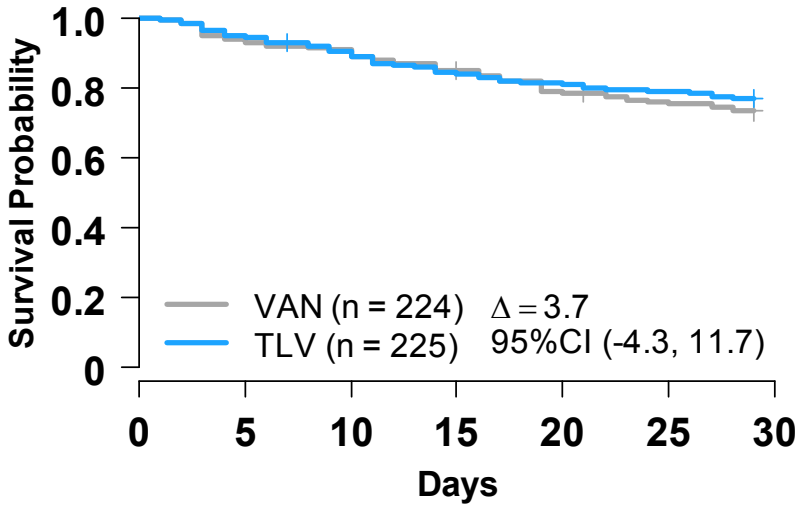
4.5.9.3.3 MPP-ATS/IDSA Population

- *The MPP-ATS/IDSA analysis group, aggregated across studies to provide statistical power for the treatment comparison, demonstrated noninferiority.*

A Kaplan-Meier survival curve for the MPP-ATS/IDSA analysis set (patients with only Gram-positive pathogens) for the aggregate of Studies 0015 and 0019 is presented in Figure 10. The aggregated studies achieved 75% power (see Table 26).

For the MPP-ATS/IDSA analysis set, noninferiority of telavancin to vancomycin in the treatment of NP was demonstrated for 28-day all-cause mortality in the aggregated studies (lower limit of 95% CI of treatment difference greater than -10%).

Figure 10: Kaplan-Meier Survival Curves – MPP-ATS/IDSA Population, Aggregated Studies 0015 and 0019



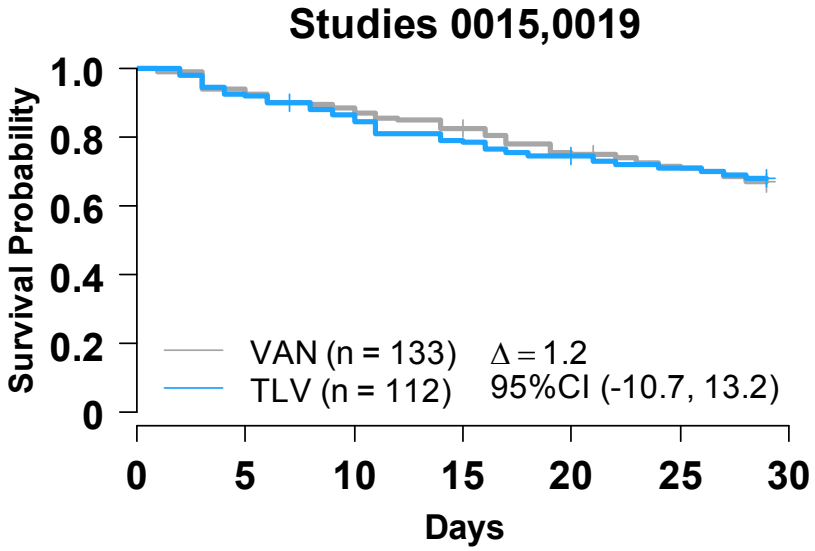
MPP = modified per protocol; ATS = American Thoracic Society; IDSA = Infectious Disease Society of America; VAN = vancomycin; TLV = telavancin; CI = confidence interval.

4.5.9.3.4 MMRSA-ATS/IDSA Population

A Kaplan-Meier survival curve for the MMRSA-ATS/IDSA analysis set (patients with only MRSA) for the aggregate of Studies 0015 and 0019 is presented in Figure 11. The aggregated studies achieved 50% power (see Table 26).

The 28-day survival estimates were similar between the two treatment groups (1.2% difference favoring telavancin); however, noninferiority was not demonstrated in the MMRSA-ATS/IDSA analysis set owing to a relative small sample size in this population.

Figure 11: Kaplan-Meier Survival Curves – MMRSA-ATS/IDSA Population, Aggregated Studies 0015 and 0019



MMRSA = modified methicillin-resistant *S. aureus*; ATS = American Thoracic Society; IDSA = Infectious Disease Society of America; VAN = vancomycin; TLV = telavancin; CI = confidence interval.

4.5.9.3.5 Mortality Analysis by Baseline Renal Function

- *A treatment interaction between pretreatment level of CrCL < 30 mL/min and treatment group showed a higher rate of mortality in the telavancin group.*
- *No difference in mortality outcomes was observed in patients with baseline CrCL ≥ 30 mL/min.*

Exploratory proportional hazards regression analyses were used to (1) identify prognostic factors associated with mortality using the AT analysis groups, and (2) check each prognostic factor for interaction with treatment. The prognostic variables were identified individually and independent of treatment. There were 18 nominally statistically significant variables identified from the combined data for Studies 0015 and 0019, ignoring treatment. An interaction was identified between "treatment with telavancin" and "presence of investigator-defined ARF at baseline," wherein patients with ARF at treatment initiation had substantially higher mortality rates than patients who did not have ARF in both treatment groups, but also that telavancin-treated patients had higher mortality rates than vancomycin-treated patients. Because no specific clinical definition for ARF was provided per protocol, an objective definition of the impacted population was sought. Analyses of mortality by renal function (CrCL) category (< 30 mL/min, 30 to < 50 mL/min, 50 to < 80 mL/min and ≥ 80 mL/min) a prespecified group of interest in the SAP were conducted to identify a more objective definition for severe renal impairment. The difference in mortality at 28 days in the severe renal impairment cohort was higher in the telavancin group than the vancomycin group, compared with almost identical and noninferior all-cause

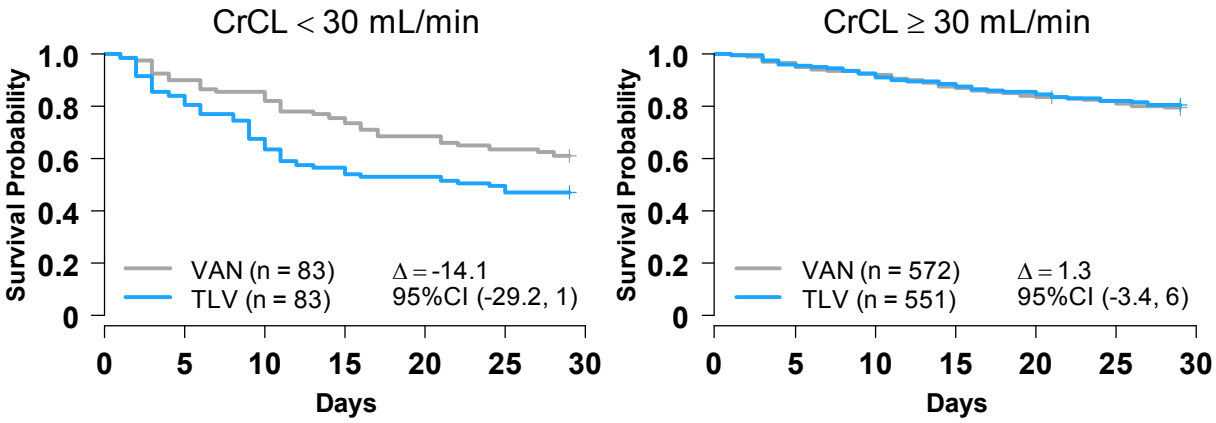
mortality rates for both groups among patients with CrCL ≥ 30 mL/min. The treatment interaction with severe baseline renal impairment was stronger than the ARF interaction. Therefore, CrCL categorization has been used for exploratory analyses by baseline renal function.

Kaplan-Meier survival curves by baseline renal function (CrCL < 30 mL/min and ≥ 30 mL/min) in the AT-ATS/IDSA, PP-ATS/IDSA, and MPP-ATS/IDSA analysis sets are presented in Figure 12, Figure 13, and Figure 14, respectively.

In both treatment groups, survival rates were markedly lower in patients with baseline severe renal dysfunction (baseline CrCL < 30 mL/min, ie, at treatment initiation). However, the survival rates in the telavancin group with severe renal dysfunction were approximately 14% lower than in the vancomycin group.

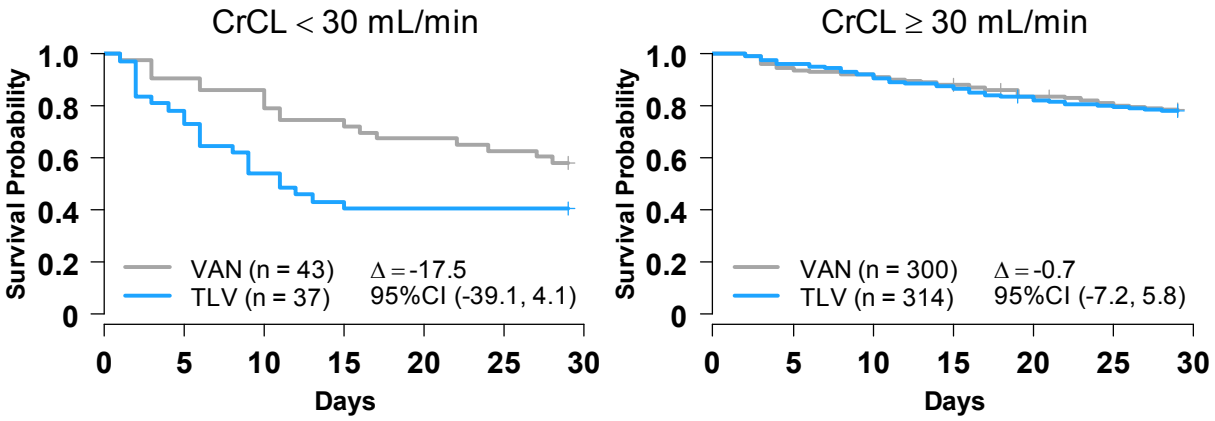
For patients with CrCL ≥ 30 mL/min in all three analysis sets, noninferiority was demonstrated for telavancin by the lower bound of the 95% CI of the treatment difference greater than -10%.

Figure 12: Kaplan-Meier Survival Curves by Baseline Renal Function – AT-ATS/IDSA Population, Aggregated Studies 0015 and 0019



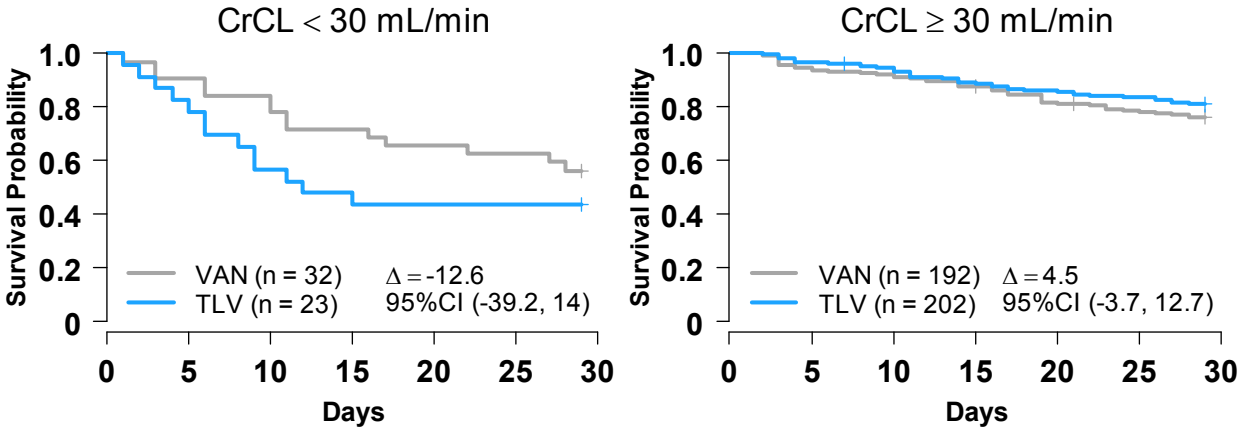
AT = all-treated; ATS = American Thoracic Society; IDSA = Infectious Disease Society of America; CrCL = creatinine clearance; CI = confidence interval; VAN = vancomycin; TLV = telavancin.

Figure 13: Kaplan-Meier Survival Curves by Baseline Renal Function – PP-ATS/IDSA Population, Aggregated Studies 0015 and 0019



PP = per protocol; ATS = American Thoracic Society; IDSA = Infectious Disease Society of America; CrCL = creatinine clearance; CI = confidence interval; VAN = vancomycin; TLV = telavancin.

Figure 14: Kaplan-Meier Survival Curves by Baseline Renal Function – MPP-ATS/IDSA Population, Aggregated Studies 0015 and 0019



MPP = modified per protocol; ATS = American Thoracic Society; IDSA = Infectious Disease Society of America; CrCL = creatinine clearance; CI = confidence interval; VAN = vancomycin; TLV = telavancin.

4.5.9.4 Additional (Sensitivity) Analysis of Mortality

Sensitivity analyses were conducted to evaluate the impact on 28-day all-cause mortality of various modifications, such as excluding patients in the analysis subgroups based on the following:

- Received potentially effective concomitant antibiotic (PEA) therapy

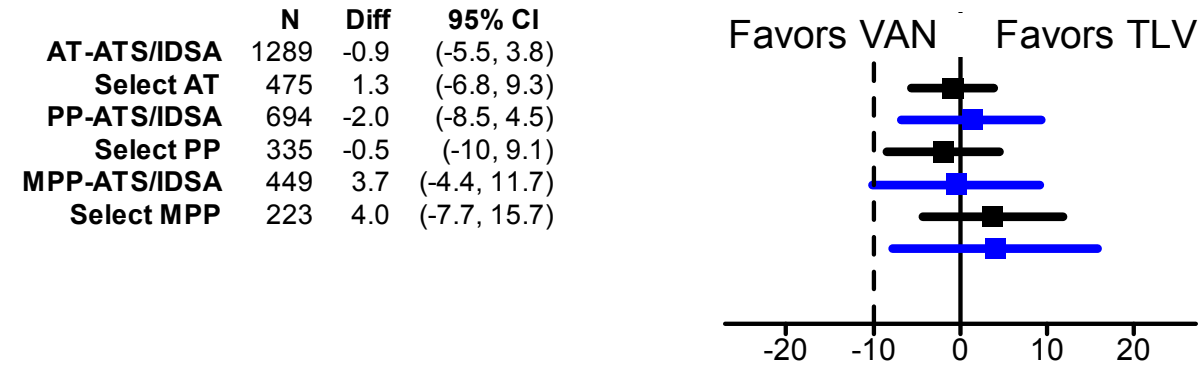
- Did not have reliable respiratory samples
- Had specific levels of renal function (as presented above in Section 4.5.9.3.5)
- Did not have radiographic evidence of pneumonia

Because very few patients did not have confirmed radiographic evidence of pneumonia, this parameter was not included, as it would have had little impact.

Figure 15 displays point estimates of mortality difference and 95% CIs for the key analysis groups unadjusted for renal function, reliable respiratory samples and the administration of PEA therapy as well as the same analysis groups adjusted by excluding patients who did not have reliable respiratory samples and who received PEA ("Select" group). As can be seen across all three analysis groups, the exclusion of these parameters had either no effect or slightly increased the treatment difference in favor of telavancin.

Figure 16 displays the same plot as discussed above but for patients with baseline CrCL ≥ 30 mL/min. As for all patients, little impact of these exclusions was observed in the analysis groups.

Figure 15: Survival Differences for Key Analysis Groups – All Patients, Aggregated Studies 0015 and 0019

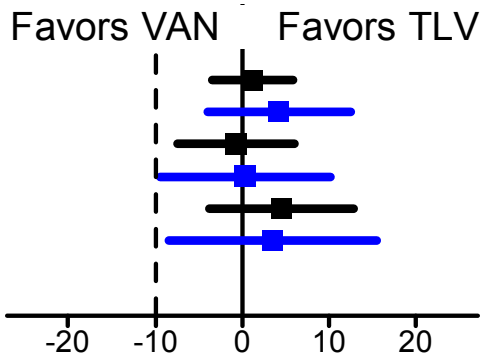


Note: Select = ATS/IDSA, reliable and adjudicated sample, and no PEA.
VAN = vancomycin; TLV = telavancin; CI = confidence interval; AT = all-treated; ATS = American Thoracic Society; IDSA = Infectious Disease Society of America; PP = per protocol; MPP = modified per protocol.

Figure 16: Survival Differences for Key Analysis Groups – Patients With Baseline CrCL ≥ 30, Aggregated Studies 0015 and 0019

Studies 0015,0019

	N	Diff	95% CI
AT-ATS/IDSA	1123	1.2	(-3.5, 6)
Select AT	408	4.2	(-4, 12.5)
PP-ATS/IDSA	614	-0.7	(-7.3, 5.9)
Select PP	294	0.3	(-9.5, 10.1)
MPP-ATS/IDSA	394	4.5	(-3.7, 12.7)
Select MPP	193	3.5	(-8.5, 15.4)



Note: Select = ATS/IDSA, reliable and adjudicated sample, and no PEA.
CrCL = creatinine clearance; VAN = vancomycin; TLV = telavancin; CI = confidence interval; AT = all-treated; ATS = American Thoracic Society; IDSA = Infectious Disease Society of America; PP = per protocol; MPP = modified per protocol.

4.5.10 Efficacy Conclusions

- *Telavancin demonstrated noninferiority compared with vancomycin upon examination of the prespecified clinical response endpoint in two adequate, well-controlled studies.*
- *Significantly higher cure rates were observed in the telavancin group for patients with monomicrobial S. aureus infections, in patients with S. aureus with higher vancomycin MIC values, and in patients with VAP.*
- *The results based on the patients' clinical response were supported by supplemental post-hoc analyses of 28-day mortality.*

The results of the primary efficacy endpoint, clinical response at the TOC, in the coprimary AT and in the CE analysis populations consistently showed that telavancin was noninferior to vancomycin in patients with NP. Significantly higher cure rates were observed in the telavancin group for patients with monomicrobial *S. aureus* infections (both MRSA and MSSA), in patients with *S. aureus* with higher (≥ 1 µg/mL) vancomycin MIC values, and in patients with VAP.

In patients with mixed infections, cure rates were numerically lower in the telavancin group than in the vancomycin group; this could be due to the higher proportion of patients in the telavancin group compared with the vancomycin group either did not have their Gram-negative pathogens eradicated or who developed possible Gram-negative superinfections.

Telavancin demonstrated noninferiority to vancomycin, which was met when the lower bounds of the 95% CI was greater than -0.10, for the post-hoc 28-day all-cause mortality endpoint for each study (Studies 0015 and 0019) and their aggregate in the primary

AT-ATS/IDSA analysis set. Noninferiority was also demonstrated in both the PP-ATS/IDSA and MPP-ATS/IDSA analysis sets.

Sensitivity analyses were conducted to evaluate the impact on 28-day all-cause mortality of various modifications to the data sets that would exclude certain patients who had, for example, potentially unreliable respiratory samples or who had received concomitant PEA therapy. The results of these analyses supported the demonstrated efficacy of telavancin.

Patients treated with telavancin in the AT-ATS/IDSA, PP-ATS/IDSA, and MPP-ATS/IDSA analysis sets with baseline CrCL < 30 mL/min had significantly higher mortality rates than patients with CrCL ≥ 30 mL/min.

4.6 Clinical Safety Overview

- *A mortality risk was observed in the telavancin group in patients with baseline CrCL <30 mL/min, or with declines from ≥ 30 mL/min to < 30 mL/min during treatment.*
- *As with vancomycin treatment, patients should have their renal function monitored carefully, with appropriate dosage adjustments made if renal function declines and, consideration given to continuing telavancin if the anticipated benefit to the patient outweighs the potential risk, or discontinuation if other appropriate options for treatment are available.*
- *The incidence of most AEs was similar or lower on telavancin with the exception of renal events; compared with vancomycin, telavancin has an increased rate of renal AEs.*
- *No other new safety signals emerged during the NP trials that are not well described in the approved product labeling.*

4.6.1 Safety Analysis Population

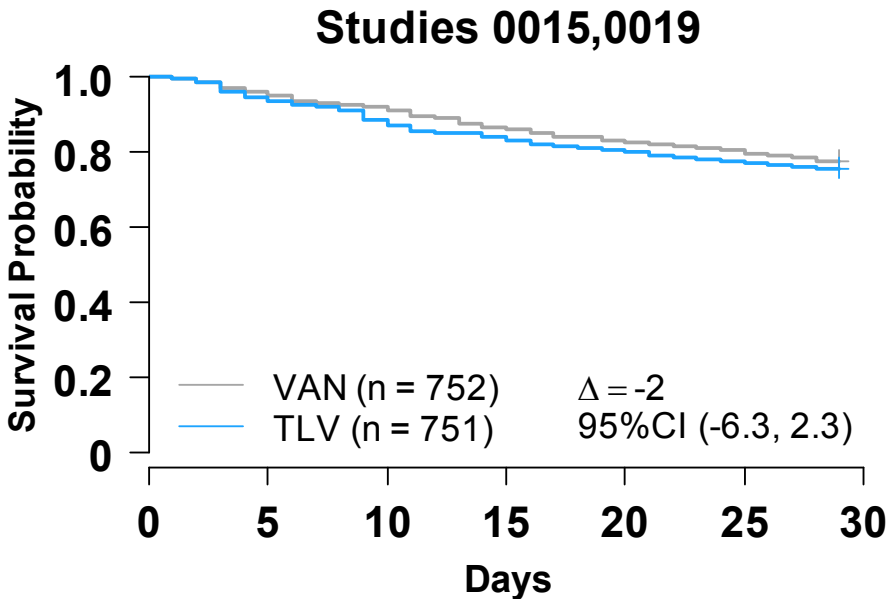
The Safety Population includes all patients treated in the NP clinical studies evaluating telavancin 10 mg/kg once daily. The mean duration of treatment was 9.5 ± 4.7 days in the telavancin group and 9.7 ± 4.5 days in the vancomycin group.

For the following general safety analysis, the 2 patients in the NP studies who were randomized to vancomycin but inadvertently given telavancin are included in the telavancin population (ie, as treated). Therefore, the total number of patients exposed to study medication in the Phase 3 studies for NP was 751 patients in the telavancin treatment group and 752 patients in the vancomycin group.

4.6.2 Overview of Deaths

A Kaplan-Meier survival curve for the Safety Population for Studies 0015 and 0019 in aggregate are presented in Figure 17.

Figure 17: Kaplan-Meier Survivial Curve – Safety Population, Aggregated Studies 0015 and 0019



VAN = vancomycin; TLV = telavancin; CI = confidence interval.

Table 28 displays the investigator-assessed causes of death in patients in the Safety Population for Studies 0015 and 0019. Of the 342 patients who died in the 28-day window, causes of death were missing for 24 patients. All except one of the unknown causes of death occurred on or after Study Day 10, and two-thirds occurred very late (Day 20 or later). Moreover, the cure rates at the TOC visit for these patients with an unknown cause of death were 57% for the telavancin group and 40% for the vancomycin group, supporting the hypothesis of death due to underlying condition as opposed to a lack of efficacy.

In general, the causes were similar between the treatment groups and across the studies, except for an imbalance in MOF and sepsis/septic shock, which occurred more frequently among patients treated with telavancin. This is explored further in Section 4.6.5.

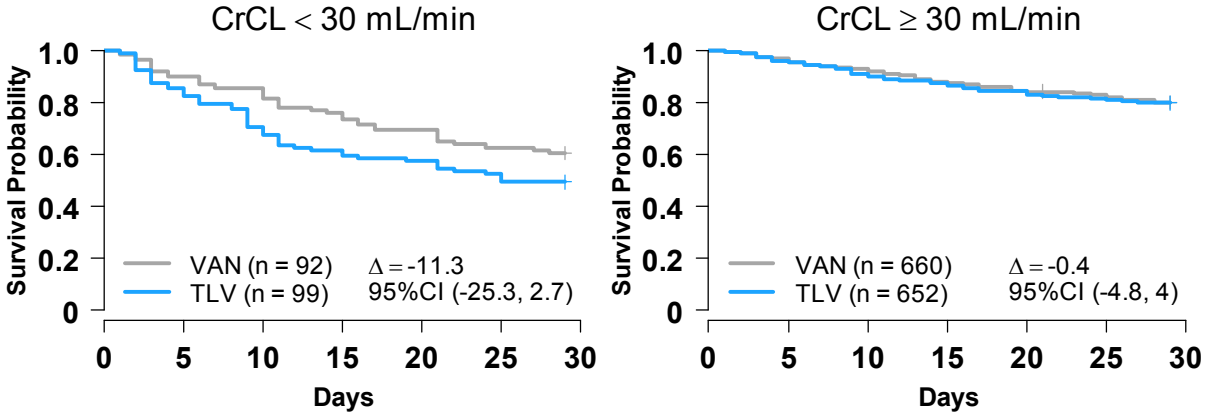
Table 28: Cause of Death – Safety Population, Aggregated Studies 0015 and 0019

Cause of Death	TLV n = 751	VAN n = 752
Renal-Related	4 (1%)	2 (< 1%)
Sepsis / Shock	38 (5%)	30 (4%)
MOF	19 (3%)	8 (1%)
Respiratory-Related (Non-NP)	28 (4%)	28 (4%)
NP	22 (3%)	27 (4%)
Fungus / Nonrespiratory Infection	5 (1%)	3 (< 1%)
Cardiac / Cerebrovascular	40 (5%)	44 (6%)
Gastrointestinal	4 (1%)	5 (1%)
Other	5 (1%)	6 (1%)
Unknown Cause	14 (2%)	10 (1%)
Total	179 (24%)	163 (22%)

Unknown deaths: Day 3 (n = 1); ≥ Day 10 (n = 23); ≥ Day 20 (n =16)
TLV = telavancin; VAN = vancomycin; MOF = multiorgan failure; NP = nosocomial pneumonia.

As noted above, proportional hazards regression analyses revealed an interaction between the characteristics “treatment with telavancin” and baseline severe renal impairment (CrCL < 30 mL/min at treatment initiation, Figure 18). The difference in mortality at 28 days in the severe renal impairment cohort was approximately 11% higher in the telavancin group than the vancomycin group, compared with almost identical rates for both groups among patients with CrCL ≥ 30 mL/min.

Figure 18: Kaplan-Meier Survival Curves – Safety Population by Baseline CrCL Category, Studies 0015 and 0019



AT = all-treated; CrCL = creatinine clearance; CI = confidence interval; VAN = vancomycin; TLV = telavancin.

Theravance conducted intensive and comprehensive exploratory modeling using Cox proportional hazards models, logistic regression models, and decision trees to describe the

variation in the current study population for factors that were explanatory for the all-cause mortality outcome. Multiple factors associated with renal function were consistently identified across all models as having significant treatment interactions, with CrCL being of primary significance. Decision trees determined an optimal threshold of CrCL < 33 mL/min for association with increased mortality risk. As this was very close to a dose adjustment threshold of CrCL < 30 mL/min, which is used for many drugs, it was believed that using CrCL < 30 mL/min represents an acceptable balance of statistical modeling and clinical utility.

Table 29 displays the investigator-assessed causes of death for those patients with baseline severe renal dysfunction (CrCL < 30 mL/min at treatment initiation). Again, the causes listed were very similar between the treatment groups, with the exception of higher incidence of MOF in the telavancin group. The SAEs of MOF and sepsis/septic shock are explored further below in Section 4.6.5. The deaths from unknown cause largely occurred late in the 28-day period.

Table 29: Cause of Death – Safety Population with Baseline CrCL < 30 mL/min, Aggregated Studies 0015 and 0019

Cause of Death	TLV n = 99	VAN n = 92
Renal	2 (2%)	0
Sepsis / Shock	8 (8%)	9 (10%)
MOF	10 (10%)	3 (3%)
Respiratory-Related (Non-NP)	9 (10%)	7 (7%)
NP	6 (6%)	5 (5%)
Fungus / Nonrespiratory Infection	1 (1%)	0
Cardiac / Cerebrovascular	8 (8%)	8 (9%)
Gastrointestinal	1 (1%)	0
Other	2 (2)	1 (1%)
Unknown Cause	3 (3%)	3 (3%)

Unknown deaths: ≥ Day 10 (n = 6); ≥ Day 20 (n = 4).
TLV = telavancin; VAN = vancomycin; MOF = multiorgan failure; NP = nosocomial pneumonia.

Multiorgan Failure Deaths

The distribution of baseline pathogens was examined for those patients who died of MOF and reveals that, among the 10 patients in the telavancin group, 3 patients had no baseline pathogens recovered, 5 had Gram-negative pathogens only (*P. aeruginosa, S. maltophilia*) or mixed infection, and 2 had only Gram-positive baseline pathogens.

These 2 MOF deaths in the telavancin group with Gram-positive baseline pathogens included 1 diabetic patient with MSSA NP who had a good clinical and microbiologic response, but died after discontinuation of treatment following arterial emboli in an already ischemic leg. The other patient had MRSA NP but died 15 hours after the first dose of study

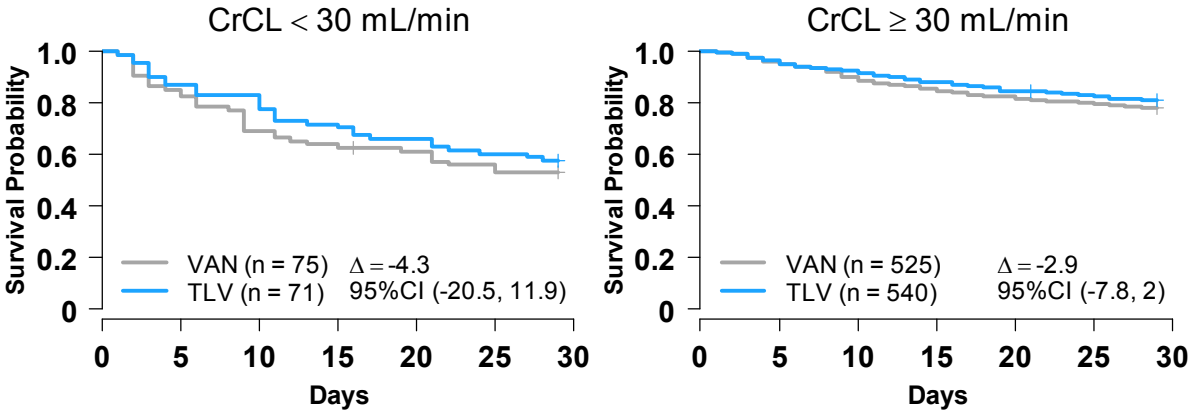
medication. This patient was admitted with congestive heart failure, acute on chronic renal failure, and chronic lung disease with respiratory failure.

Thus, the higher rate of MOF in the telavancin group as a cause of death among patients with severe renal impairment at baseline does not appear to be due to inadequate treatment of Gram-positive NP, but rather more to Gram-negative infections. It is also possible that renal toxicity due to telavancin may have contributed to the organ failures.

However, given these findings, patients with Gram-negative infections only were excluded from the above analysis. The Kaplan-Meier plots for the remainder of the patients are displayed in Figure 19. Survival at 28 days was more similar (~4% difference) in the two treatment groups with baseline CrCL < 30 mL/min, supporting the contention that the higher mortality rates in this population are not due to inadequate treatment of Gram-positive NP, but rather more likely to Gram-negative infections.

Additional evidence is provided when examining the causes of death among this cohort of patients with Gram-negative infections excluded. Table 30 displays the causes of death in the cohort, and here deaths due to NP are similar in the two groups, as are deaths due to MOF and sepsis/shock, again supporting the contention that failure to treat the Gram-positive infection under study does not appear to be the reason for any mortality risk in this set of patients with baseline severe renal impairment. There were 2 patients in the telavancin group who died of renal events compared with none in the vancomycin group.

Figure 19: Kaplan-Meier Survival Curves – Safety Population by Baseline CrCL Category, Patients with Only Gram-Negative Infections Excluded, Studies 0015 and 0019



CrCL = creatinine clearance; CI = confidence interval; VAN = vancomycin; TLV = telavancin.

Table 30: Cause of Death Among Patients with Baseline CrCL < 30 mL/min, Excluding Patients with Only Gram-Negative Infections – Safety Population, Studies 0015 and 0019

Cause of Death	TLV n = 75	VAN n = 71
Cardiac/Cardiovascular	6	7
Gastrointestinal	1	0
MOF	7	3
NP	4	5
Other	2	0
Renal	2	0
Respiratory	8	6
Sepsis/Shock	4	7
Unknown	1	2
Total Deaths	35	30

CrCL = creatinine clearance; AT = all-treated; TLV = telavancin; VAN = vancomycin; MOF = multiorgan failure; NP = nosocomial pneumonia.

There is no ready explanation for an association between telavancin and higher mortality rates in patients with baseline severe renal impairment. Although it is tempting to postulate a relationship between the nephrotoxicity associated with use of telavancin and the risk for increased mortality in patients with baseline severe renal impairment, no clear link has been established after examining the case histories for these patients. There are data suggesting an excess of deaths due to Gram-negative infections. In an abundance of caution and concern for patient safety, the proposed labeling warns against the use of telavancin in patients with baseline severe renal impairment unless the anticipated benefit to the patient outweighs the potential risk.

4.6.3 Overview of Adverse Events

Table 31 presents an overview of AEs in the Phase 3 NP studies, both individually and in the aggregate, including the number of patients who experienced at least one AE or SAE, or discontinued study medication due to an AE. Of the 751 patients treated with telavancin 10 mg/kg (or a dosage adjusted for renal insufficiency) in the aggregate Safety Population, 616 (82%) patients experienced at least one AE and, of the 752 patients treated with vancomycin, 613 (82%) patients experienced at least one AE. SAEs were reported in 234 patients treated with telavancin (31%) compared with 197 (26%) patients treated with vancomycin. Study medication was prematurely discontinued due to an AE in 60 patients (8%) treated with telavancin compared with 40 patients (5%) treated with vancomycin.

Table 31: Overview of AEs – Safety Population, Studies 0015 and 0019

	Study 0015		Study 0019		Total	
Category	TLV (N = 372)	VAN[a] (N = 374)	TLV (N = 379)	VAN[b] (N = 378)	TLV (N = 751)	VAN[c] (N = 752)
Patients With at Least One AE	321 (86%)	317 (85%)	295 (78%)	296 (78%)	616 (82%)	613 (82%)
Patients With at Least One SAE	127 (34%)	88 (24%)	107 (28%)	109 (29%)	234 (31%)	197 (26%)
Patients Who Discontinued Study Medication Due to AE	33 (9%)	17 (5%)	27 (7%)	23 (6%)	60 (8%)	40 (5%)

AE = adverse event; TLV = telavancin; VAN = vancomycin; SAE = serious adverse event.
[a] Includes 9 patients who received an antistaphylococcal penicillin instead of vancomycin.
[b] Includes 11 patients who received an antistaphylococcal penicillin instead of vancomycin.
[c] Includes 20 patients who received an antistaphylococcal penicillin instead of vancomycin.

4.6.4 Common Adverse Events in Nosocomial Pneumonia Studies

AEs that were reported for ≥ 5% of patients in either the telavancin or vancomycin group of the aggregated Safety Population are presented in Table 32.

Diarrhea, constipation, anemia, hypokalemia, and hypotension were the most frequently reported (> 5%) AEs for patients treated with telavancin the Safety Population, whereas for patients treated with vancomycin, diarrhea, anemia, hypokalemia, constipation, hypotension, insomnia, and decubitus ulcer were the most frequently reported.

In the aggregated Safety Population, AEs assessed by the investigator as possibly/probably related to study medication were reported in 28% of patients treated with telavancin and 23% of patients treated with vancomycin. The most commonly reported (> 1%) possibly/probably related AEs in the telavancin group were diarrhea (4%), nausea (2%), vomiting (2%), renal failure acute (2%), alanine aminotransferase (ALT) increased (2%), blood creatinine increased (2%), and rash (2%). All other AEs considered possibly/probably related to study medication were reported in ≤ 1% of patients treated with telavancin. In the vancomycin group, the most commonly reported (> 1%) AEs considered possibly/probably related were diarrhea (3%) and ALT increased (2%). All other AEs considered possibly/probably related to study medication were reported in ≤ 1% of patients treated with vancomycin.

Table 32: AEs with an Incidence of ≥ 5% in Telavancin or Vancomycin – Safety Population, Aggregated Studies 0015 and 0019

MedDRA SOC Preferred Term	TLV (N = 751)	VAN (N = 752)
Body System As A Whole		
Peripheral Edema	5%	5%
Blood and Lymphatic System Disorders		
Anemia	9%	11%
Cardiovascular Disorders		
Atrial Fibrillation	4%	5%
Gastrointestinal Disorders		
Nausea	5%	4%
Vomiting	5%	4%
Constipation	9%	9%
Diarrhea	11%	12%
Metabolism and Nutrition Disorders		
Hypokalaemia	8%	11%
Psychiatric Disorders		
Insomnia	5%	6%
Renal Disorders		
Acute Renal Failure	5%	4%
Skin and Subcutaneous Tissue Disorders		
Decubitus Ulcer	5%	6%
Vascular Disorders		
Hypotension	6%	7%

AE = adverse event; SOC = system organ class; MedDRA = Medical Dictionary for Regulatory Activities; TLV = telavancin; VAN = vancomycin.

The occurrence of AEs generally regarded as infusion-associated reactions or hypersensitivity reactions, including urticaria, pruritus, and rash, was similar between the telavancin and vancomycin treatment groups. Rash occurred in 33 patients (4%) treated with telavancin and 26 patients (3%) treated with vancomycin, pruritus occurred in 4 patients (< 1%) treated with telavancin and 6 patients (< 1%) treated with vancomycin, and urticaria occurred in 0 patients treated with telavancin and in 1 patient (< 1%) treated with vancomycin. One case of “red-man syndrome” was reported in a telavancin-treated patient, a 91-year-old white female, who was hospitalized for COPD exacerbation. Prior to study entry she had received treatment with ceftriaxone and piperacillin/tazobactam for pneumonia. On Study Day 5 she experienced mild AEs of red man syndrome and anxiety. The anxiety resolved that day and the red man syndrome resolved the next day (Study Day 6) despite continuation of study treatment. The red man syndrome was considered possibly/probably related to study medication by the investigator.

4.6.5 Serious Adverse Events

A summary of treatment-emergent SAEs that occurred at an incidence of ≥ 1% in either aggregate treatment group is presented in Table 33. Within the aggregated Safety Population, at least one treatment-emergent SAE was reported in 234 patients (31%) treated with telavancin and 197 patients (26%) treated with vancomycin. The most frequently reported SAE was septic shock, which was experienced by 4% of patients in both treatment groups. MOF, renal failure acute, and sepsis were experienced in more patients treated with telavancin than patients treated with vancomycin (difference between treatment groups was 1% in each case).

In patients treated with telavancin, the most commonly reported treatment-emergent SAEs included septic shock (30 patients, 4%), MOF (24 patients, 3%), respiratory failure (21 patients, 3%), renal failure acute (18 patients, 2%), sepsis (12 patients, 2%), and pneumonia (10 patients, 1%). In patients treated with vancomycin, the most commonly reported treatment-emergent SAEs were septic shock (28 patients, 4%), respiratory failure (22 patients, 3%), MOF (14 patients, 2%), pneumonia (14 patients, 2%), renal failure acute (11 patients, 1%), cardiac failure congestive (10 patients, 1%), sepsis (9 patients, 1%), and acute respiratory failure (8 patients, 1%).

Table 33: Treatment-Emergent SAEs (≥ 1% in Either Aggregate Treatment Group) – Safety Population, Studies 0015 and 0019

	0015		0019		Total	
MedDRA SOC Preferred Term	**TLV (N = 372)**	**VAN[a] (N = 374)**	**TLV (N = 379)**	**VAN[b] (N = 378)**	**TLV (N = 751)**	**VAN[c] (N = 752)**
Any Serious Event	127 (34%)	88 (24%)	107 (28%)	109 (29%)	234 (31%)	197 (26%)
Cardiac Disorders						
Any Serious Event	18 (5%)	21 (6%)	12 (3%)	20 (5%)	30 (4%)	41 (5%)
Cardiac Failure Congestive	4 (1%)	3 (< 1%)	0	7 (2%)	4 (< 1%)	10 (1%)
General Disorders and Administration Site Conditions						
Any Serious Event	13 (3%)	9 (2%)	13 (3%)	6 (2%)	26 (3%)	15 (2%)
MOF	11 (3%)	8 (2%)	13 (3%)	6 (2%)	24 (3%)	14 (2%)
Infections and Infestations						
Any Serious Event	32 (9%)	29 (8%)	37 (10%)	32 (8%)	69 (9%)	61 (8%)
Pneumonia	6 (2%)	8 (2%)	4 (1%)	6 (2%)	10 (1%)	14 (2%)
Sepsis	6 (2%)	4 (1%)	6 (2%)	5 (1%)	12 (2%)	9 (1%)
Septic Shock	13 (3%)	13 (3%)	17 (4%)	15 (4%)	30 (4%)	28 (4%)
Renal and Urinary Disorders						
Any Serious Event	15 (4%)	7 (2%)	9 (2%)	9 (2%)	24 (3%)	16 (2%)
Renal Failure Acute	11 (3%)	3 (< 1%)	7 (2%)	8 (2%)	18 (2%)	11 (1%)
Respiratory, Thoracic and Mediastinal Disorders						
Any Serious Event	33 (9%)	27 (7%)	28 (7%)	30 (8%)	61 (8%)	57 (8%)
Acute Respiratory Failure	1 (< 1%)	4 (1%)	3 (< 1%)	4 (1%)	4 (< 1%)	8 (1%)
Respiratory Failure	14 (4%)	11 (3%)	7 (2%)	11 (3%)	21 (3%)	22 (3%)

Note: All SAEs include SAEs that resulted in death.

SAE = serious adverse event; TLV = telavancin; VAN = vancomycin; MedDRA = Medical Dictionary for Regulatory Activities; SOC = system organ class; MOF = multiorgan failure.

[a] Includes 9 patients who received an antistaphylococcal penicillin instead of vancomycin.

[b] Includes 11 patients who received an antistaphylococcal penicillin instead of vancomycin.

[c] Includes 20 patients who received an antistaphylococcal penicillin instead of vancomycin.

Because appropriate antibiotic therapy has been shown to have a significant impact on mortality in NP, we explored the effects of administration of inadequate antibiotic therapy (as defined in Section 4.4.5) to patients who experienced MOF and sepsis/septic shock which, as noted above, frequently were listed as the cause of death.

Table 34 displays the effect of the frequency of these AEs in patients who either did or did not receive adequate Gram-negative coverage. When adequate Gram-negative coverage was applied, the imbalance between the groups was greatly minimized, with the majority of the imbalance residing in the group of patients who did not receive adequate Gram-negative coverage.

Table 34: Patients with MOF or Sepsis/Septic Shock as an AE, Overall and by Adequacy of Gram-Negative Coverage – Safety Population, Aggregated Studies 0015 and 0019

No. of Patients	TLV (N = 751)	VAN (N = 752)
AE of MOF or Sepsis/Septic Shock	77 (10.3%)	54 (7.2%)
Adequate Gram-Negative Coverage	47 (6.3%)	42 (5.6%)
Inadequate Gram-Negative Coverage	30 (4.0%)	12 (1.6%)

MOF = multiorgan failure; AE = adverse event; TLV = telavancin; VAN = vancomycin.

4.6.6 Discontinuation of Study Medication Due to an Adverse Event

Table 35 presents a summary of AEs reported in more than one patient in either treatment group, which resulted in discontinuation of study medication in the Phase 3 NP studies. In the aggregate Safety Population, a total of 100 patients, 60 (8%) patients in the telavancin group and 40 (5%) patients in the vancomycin group, had at least one AE that resulted in discontinuation of study medication. The higher incidence of discontinuations in the telavancin group compared with the vancomycin group was primarily attributed to the difference between treatment groups in Study 0015. By SOC, the most frequent AEs leading to discontinuation of study medication were in the Infections and Infestations, Investigations, and Renal and Urinary Disorders SOCs. The AEs that led to discontinuation of study medication in more patients treated with telavancin (4 or more patients) than patients treated with vancomycin in the aggregate Safety Population included renal failure acute (9 telavancin patients, 2 vancomycin patients), ECG QTc interval prolonged (8 telavancin patients, 2 vancomycin patients), and blood creatinine increased (5 telavancin patients, 1 vancomycin patients). Conversely, septic shock (1 telavancin patient, 5 vancomycin patients) and MOF (1 telavancin patient, 4 vancomycin patients) were more frequent in patients treated with vancomycin than patients treated with telavancin.

Table 35: Patients with AEs Resulting in Discontinuation of Study Medication – Safety Population, Studies 0015 and 0019

	0015		0019		Total	
MedDRA SOC Preferred Term	**TLV (N = 372)**	**VAN[a] (N = 374)**	**TLV (N = 379)**	**VAN[b] (N = 378)**	**TLV (N = 751)**	**VAN[c] (N = 752)**
Any Discontinuation Event	33 (9%)	17 (5%)	27 (7%)	23 (6%)	60 (8%)	40 (5%)
Blood and Lymphatic System Disorders						
Any Discontinuation Event	1 (< 1%)	3 (< 1%)	0	1 (< 1%)	1 (< 1%)	4 (< 1%)
Thrombocytopenia	0	2 (< 1%)	0	0	0	2 (< 1%)
General Disorders and Administration Site Conditions						
Any Discontinuation Event	0	3 (< 1%)	3 (< 1%)	1 (< 1%)	3 (< 1%)	4 (< 1%)
MOF	0	3 (< 1%)	1 (< 1%)	1 (< 1%)	1 (< 1%)	4 (< 1%)
Infections and Infestations						
Any Discontinuation Event	2 (< 1%)	3 (< 1%)	7 (2%)	9 (2%)	9 (1%)	12 (2%)
Meningitis	0	0	2 (< 1%)	1 (< 1%)	2 (< 1%)	1 (< 1%)
Sepsis	2 (< 1%)	0	1 (< 1%)	1 (< 1%)	3 (< 1%)	1 (< 1%)
Septic Shock	0	3 (< 1%)	1 (< 1%)	2 (< 1%)	1 (< 1%)	5 (< 1%)
Investigations						
Any Discontinuation Event	13 (3%)	0	4 (1%)	3 (< 1%)	17 (2%)	3 (< 1%)
Blood Creatinine Increased	4 (1%)	0	1 (< 1%)	1 (< 1%)	5 (< 1%)	1 (< 1%)
ECG QTc Interval Prolonged	5 (1%)	0	3 (< 1%)	2 (< 1%)	8 (1%)	2 (< 1%)
Psychiatric Disorders						
Any Discontinuation Event	1 (< 1%)	0	1 (< 1%)	0	2 (< 1%)	0
Agitation	1 (< 1%)	0	1 (< 1%)	0	2 (< 1%)	0
Renal and Urinary Disorders						
Any Discontinuation Event	8 (2%)	3 (< 1%)	3 (< 1%)	3 (< 1%)	11 (1%)	6 (< 1%)
Renal Failure Acute	6 (2%)	0	3 (< 1%)	2 (< 1%)	9 (1%)	2 (< 1%)
Renal Impairment	0	1 (< 1%)	0	1 (< 1%)	0	2 (< 1%)
Renal Insufficiency	1 (< 1%)	2 (< 1%)	0	0	1 (< 1%)	2 (< 1%)
Respiratory, Thoracic and Mediastinal Disorders						
Any Discontinuation Event	6 (2%)	1 (< 1%)	0	2 (< 1%)	6 (< 1%)	3 (< 1%)
Respiratory Failure	2 (< 1%)	0	0	0	2 (< 1%)	0

AE = adverse event; TLV = telavancin; VAN = vancomycin; MedDRA = Medical Dictionary for Regulatory Activities; SOC = system organ class; MOF = multiorgan failure; ECG = electrocardiogram; QTc = corrected QT interval.

[a] Includes 9 patients who received an antistaphylococcal penicillin instead of vancomycin.

[b] Includes 11 patients who received an antistaphylococcal penicillin instead of vancomycin.

[c] Includes 20 patients who received an antistaphylococcal penicillin instead of vancomycin.

4.6.7 Adverse Events by Subgroup

There was no trend to suggest that telavancin has a substantially different safety profile based on sex, body mass index (BMI), race or baseline renal function (except for severe renal impairment). Higher rates of AEs were observed in both treatment groups among patients who were diabetic or elderly (≥ 65 years of age).

4.6.8 Adverse Events of Special Interest

The following sections provide detailed summaries of renal and cardiac safety, since these two organ systems were identified in preclinical studies as potentially of clinical importance.

4.6.8.1 Review of Renal Adverse Events

To assess potential effects of telavancin on the kidney, the following MedDRA preferred terms were chosen as indicators of treatment-associated effects on renal function: renal impairment, renal insufficiency, renal failure acute, renal failure chronic, and blood creatinine increased. In addition to a discussion of renal AEs and SAEs, changes in renal laboratory assessments (serum creatinine and calculated CrCL), whether identified as an AE or not, are also described.

Renal AEs were reported in 74 patients treated with telavancin (10%) and 57 patients treated with vancomycin (8%, Table 36). The most frequent renal AE was renal failure acute, followed by blood creatinine increased. Incidence of renal failure acute was 5% in the telavancin group (34 patients) and 4% in the vancomycin group (28 patients). Incidences of the remaining renal AEs were similar between treatment groups. Four patients in the telavancin group and 1 patient in the vancomycin group experienced an AE of chronic renal failure. All 5 patients had a medical history of chronic renal failure and experienced treatment-emergent worsening of chronic renal failure; 1 of the 4 telavancin-treated patients started hemodialysis 1 month before study entry, which continued.

During the limited study period of follow-up, of the 74 telavancin-treated patients who had at least one renal AE, 40 (54%) patients recovered completely, recovered with sequelae, or were improving from the renal AE at the last visit, compared with 31 of 57 (54%) patients in the vancomycin group. None of the 8 patients who died of a renal AE had normal baseline CrCL (Section 4.6.8.1.1). The majority of patients treated with telavancin (12/14 patients, 86%) who had normal baseline CrCL and had a renal AE recovered completely, recovered with sequelae, or were improving at the last visit.

Table 36: Renal AEs – Safety Population, Studies 0015 and 0019

	0015		0019		Total	
MedDRA SOC Preferred Term	**TLV (N = 372)**	**VAN[a] (N = 374)**	**TLV (N = 379)**	**VAN[b] (N = 378)**	**TLV (N = 751)**	**VAN[c] (N = 752)**
Any Event	37 (10%)	28 (7%)	37 (10%)	29 (8%)	74 (10%)	57 (8%)
Investigations						
Any Event	11 (3%)	6 (2%)	7 (2%)	6 (2%)	18 (2%)	12 (2%)
Blood Creatinine Increased	11 (3%)	6 (2%)	7 (2%)	6 (2%)	18 (2%)	12 (2%)
Renal and Urinary Disorders						
Any Event	27 (7%)	22 (6%)	30 (8%)	24 (6%)	57 (8%)	46 (6%)
Renal Failure Acute	18 (5%)	10 (3%)	16 (4%)	18 (5%)	34 (5%)	28 (4%)
Renal Failure Chronic	2 (< 1%)	1(< 1%)	2 (<1%)	0	4 (< 1%)	1 (< 1%)
Renal Impairment	2 (< 1%)	3(< 1%)	6 (2%)	4 (1%)	8 (1%)	7 (< 1%)
Renal Insufficiency	5 (1%)	8(2%)	7 (2%)	3 (< 1%)	12 (2%)	11 (1%)

Note: Includes the following preferred terms: renal failure acute, renal failure chronic, renal impairment, renal insufficiency, blood creatinine increased.

AE = adverse event; TLV = telavancin; VAN = vancomycin; MedDRA = Medical Dictionary for Regulatory Activities; SOC = system organ class.

[a] Includes 9 patients who received an antistaphylococcal penicillin instead of vancomycin.

[b] Includes 11 patients who received an antistaphylococcal penicillin instead of vancomycin.

[c] Includes 20 patients who received an antistaphylococcal penicillin instead of vancomycin.

4.6.8.1.1 Deaths Due to Renal Events

Per the investigator's assessment, a total of 8 patients died following the development of a renal AE. Five patients (3 patients in the telavancin group and 2 patients in the vancomycin group) died of renal events within the protocol-designated window for collection of AEs. In addition, 1 patient treated with telavancin and 2 patients treated with vancomycin died outside of the data capture window. The data capture window refers to the period during which deaths were systematically recorded, which was up to the Follow-up/TOC Visit or 28 days after the EOT for those patients who did not have a Follow-up Visit.

Of the 4 telavancin-treated patients who died of a renal AE (within window and out-of-window), 3 patients had moderate renal impairment and 1 patient had severe renal impairment at baseline. The telavancin-treated patient who had severe renal impairment at baseline died of chronic renal failure; the other 3 telavancin-treated patients died of acute renal failure. Of the 4 vancomycin-treated patients who died of a renal AE, 1 patient had mild renal impairment, 1 patient had moderate renal impairment, and 2 patients had severe renal impairment at baseline.

Brief narratives for these 4 patients treated with telavancin are provided as follows.

Telavancin-treated Patients

Patient 0015-38049-4187 an 80-year-old woman with a history of type 2 diabetes mellitus, congestive heart failure, and hypertension, was admitted from a nursing home to the hospital for bilateral pneumonia and septic shock. The patient received 4 days of telavancin therapy. Baseline creatinine clearance was 34 mL/min and serum creatinine was 1.2 mg/dL; the patient developed oliguria and renal failure within 24 to 48 hours after enrollment although no further creatinine values were available. The patient died on Study Day 5 due to acute renal failure. The investigator assessed the acute renal failure as not related to study medication and related to concurrent illness. A consultant nephrologist attributed the event of renal failure to a multifactorial etiology of sepsis, recent use of radiocontrast dye, and ischemic acute tubular necrosis due to hypertension.

Patient 0015-18010-4139, 75-year-old man with a history of chronic renal failure, COPD, diabetes mellitus, and hypertension, was admitted to the hospital after experiencing cardiac arrest requiring cardiopulmonary resuscitation (CPR) as well as an exacerbation of COPD. The patient had a history of chronic renal failure and was taking drugs known to cause renal impairment, such as captopril. The patient received 10 days of telavancin. His baseline creatinine clearance was 40 mL/min, and creatinine was 1.9 mg/dL. Serum creatinine began to rise on Study Day 2 and peaked at 3.0 mg/dL on Study Day 4, returning to baseline level of 1.9 mg/dL on Study Day 9. On Study Day 2, the patient experienced renal insufficiency (verbatim: renal failure), anuria, and hypoalbuminemia. Therapy with telavancin was ongoing until Study Day 11 at which time telavancin therapy was stopped due to resolution of signs and symptoms of pneumonia. On Study Day 11, serum creatinine level increased again to 3.8 mg/dL. The creatinine level decreased to 2.8 mg/dL on Study Day 21, and the patient expired on Study Day 37. The investigator assessed the renal failure and anuria as possibly related to study medication, however, the Sponsor considered this unlikely as the serum creatinine returned to baseline levels while the patient remained on therapy.

Patient 0019-18005-6035, a 77-year-old woman with a history of chronic renal failure, diabetes mellitus, severe peripheral vascular disease with right below the knee amputation, and myocardial infarction, was hospitalized for a pacemaker insertion for complete AV block. The patient received telavancin for 5 days. Baseline creatinine clearance was 15 mL/min and serum creatinine was 2.9 mg/dL. On Study Day 4, serum creatinine was 4.7 mg/dL and the patient was diagnosed with end stage chronic renal failure. Blood cultures obtained on Study Day 6 (local) were positive for *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. The patient died on Study Day 9 due to renal failure and sepsis. The investigator considered the events not related to study medication.

Patient 0019-34003-6591, a 63-year-old woman with a history of septicemia, lymphoma, and malnutrition, was admitted to the hospital for lymphoma treatment 70 days prior to starting telavancin therapy. Pretreatment creatinine clearance was 45 mL/min. On Study Day 1, the serum creatinine was abnormal at 1.6 mg/dL. Notably, the patient received amikacin for 21 days prior to enrollment. On Study Day 3, the patient withdrew consent and

refused further treatment having received a total of 3 days of telavancin therapy. The patient expired on Study Day 4 due to acute renal failure. The investigator attributed this event to concurrent illness and not related to study medication. The Sponsor agreed with these assessments, also noting that prolonged treatment with an aminoglycoside may have contributed to the renal failure.

4.6.8.1.2 Renal Serious Adverse Events

A total of 26 telavancin-treated patients (3%) and 16 vancomycin-treated patients (2%) experienced at least one renal SAE (Table 37). SAEs of renal failure acute and blood creatinine increased were experienced by more patients treated with telavancin than patients treated with vancomycin.

Table 37: Summary of Renal SAEs – Safety Population, Studies 0015 and 0019

	0015		0019		Total	
MedDRA SOC Preferred Term	**TLV (N = 372)**	**VAN[a] (N = 374)**	**TLV (N = 379)**	**VAN[b] (N = 378)**	**TLV (N = 751)**	**VAN[c] (N = 752)**
Any Serious Event	17 (5%)	7 (2%)	9 (2%)	9 (2%)	26 (3%)	16 (2%)
Investigations						
Any Serious Event	3 (< 1%)	0	0	0	3 (< 1%)	0
Blood Creatinine Increased	3 (< 1%)	0	0	0	3 (< 1%)	0
Renal and Urinary Disorders						
Any Serious Event	14 (4%)	7 (2%)	9 (2%)	9 (2%)	23 (3%)	16 (2%)
Renal Failure Acute	11 (3%)	3 (< 1%)	7 (2%)	8 (2%)	18 (2%)	11 (1%)
Renal Failure Chronic	0	0	1 (< 1%)	0	1 (< 1%)	0
Renal Impairment	0	0	0	1 (< 1%)	0	1 (<1%)
Renal Insufficiency	3 (< 1%)	4 (1%)	1 (< 1%)	0	4 (< 1%)	4 (< 1%)

Note: All SAEs include SAEs that resulted in death.

SAE = serious adverse event; TLV = telavancin; VAN = vancomycin; MedDRA = Medical Dictionary for Regulatory Activities; SOC = system organ class.

[a] Includes 9 patients who received an antistaphylococcal penicillin instead of vancomycin.

[b] Includes 11 patients who received an antistaphylococcal penicillin instead of vancomycin.

[c] Includes 20 patients who received an antistaphylococcal penicillin instead of vancomycin.

In 15 of the 26 telavancin-treated and 11 of the 16 vancomycin-treated patients who experienced a renal SAE, the SAE was considered possibly/probably related to study medication. Ten of the 26 telavancin-treated and 4 of the 16 vancomycin-treated patients had study medication discontinued due to the renal SAE. The renal SAEs led to dose reductions in 3 patients treated with telavancin: 1 patient (0015-38049-4187) had an SAE of acute renal failure that required dose reduction, but the event was not considered related to treatment. The patient subsequently died of renal failure. Of the 2 additional patients who had SAEs of renal insufficiency and who had their dose reduced (Patients 0015-05002-4327 and 0015-18010-4139), 1 patient completely recovered while the second patient's condition

was still present and unchanged at the last study visit. The renal SAEs led to dose reductions in 7 of the 16 patients treated with vancomycin.

All patients treated with telavancin with renal SAEs had comorbid conditions or events that may have contributed to the development or worsening of renal impairment. Notably, 12 of the 26 patients with renal SAEs had pre-existing conditions, such as chronic renal failure or acute renal failure. Congestive heart failure (10 patients) and diabetes mellitus (9 patients) were also common antecedent conditions. Sepsis and hypotension were the most common comorbid events, occurring in 15 of the 26 patients with renal SAEs. These episodes were severe enough to require the use of vasopressor medications to maintain hemodynamic stability in most patients.

Similar to telavancin, the majority of patients treated with vancomycin had underlying comorbid conditions or events that may have contributed to the development of renal impairment (worsening renal function). Six of the 16 patients had evidence of renal impairment before enrollment in the study, with 3 patients having renal insufficiency at baseline, 2 patients with acute renal failure, and 1 patient with elevated blood creatinine. In contrast to telavancin, 3 vancomycin-treated patients (0015-30905-4237, 0019-20014-6423, and 0019-07003-6320) had no underlying condition that may have contributed to the development of renal impairment; however, 2 of the patients did receive medications (nonsteroidal anti-inflammatory drugs [NSAIDs], angiotensin converting enzyme [ACE]-inhibitors) that may have contributed. Sepsis/hypotension occurred in 5 patients, congestive heart failure in 3 patients, and diabetes in 2 patients.

4.6.8.1.3 Renal Adverse Events Resulting in Early Discontinuation of Study Medication

Renal impairment was reported as an AE resulting in discontinuation of study medication in 14 telavancin-treated patients (1.9%) and 7 vancomycin-treated patients (0.9%) in NP studies.

Renal AEs that led to discontinuation of study medication were considered possibly/probably related to study medication by the Investigator in 12 of the 14 patients treated with telavancin and in 6 of the 7 patients treated with vancomycin.

Of the 14 patients treated with telavancin who discontinued study medication due to a renal AE, renal AEs resolved completely in 8 patients and resolved with sequelae in another 3 patients. In the remaining 3 patients, the renal AE that resulted in discontinuation was still present and unchanged.

Of the 7 vancomycin-treated patients who discontinued study medication due to a renal AE, the event resolved completely in 1 patient and was improving in another patient. Of the remaining 5 patients, the renal AEs that resulted in study medication discontinuation were present and unchanged in 4 patients and the fifth patient died due to an AE of renal insufficiency as discussed below.

To summarize, more patients receiving telavancin than receiving vancomycin discontinued study medication due to renal AEs. Qualitatively, however, the nature of these events, including onset time after initiation of treatment, level of renal impairment achieved, and response to discontinuation of study medication, was similar for the two treatment groups.

4.6.8.1.4 Renal Clinical Laboratory Abnormalities

In the aggregated Safety Population, more patients with normal baseline renal function, treated with telavancin (14%) than patients treated with vancomycin (9%) developed a PCS change in serum creatinine (defined as a maximum on-study value ≥ 133 µmol/L [1.5 mg/dL] that was at least 1.5-fold greater than baseline). The majority of patients had a maximum value of serum creatinine of < 3.0 mg/dL (265 µmol/L).

Table 38: Incidence of PCS Abnormalities and Changes from Baseline in Renal Function Tests in Patients with Normal Baseline Renal Function – Safety Population, Studies 0015 and 0019

	0015 + 0019 Total			
	TLV		VAN[c]	
Parameter and PCS Criteria	Patients with Values[a]	Abnormal[b] N (%)	Patients with Values[a]	Abnormal[b] N (%)
Serum Creatinine				
Maximum Change from Baseline				
Any Post-Baseline Creatinine ≥ 133 umol/L and at Least 50% Greater than Baseline	599	84 (14)	604	55 (9)
Highest Post-Baseline Result				
133 umol/L − < 177 umol/L and at Least 50% Greater than Baseline	599	28 (5)	604	28 (5)
177 umol/L − < 265 umol/L and at Least 50% Greater than Baseline	599	29 (5)	604	14 (2)
265 umol/L − < 442 umol/L and at Least 50% Greater than Baseline	599	22 (4)	604	6 (< 1)
≥ 442 umol/L and at Least 50% Greater than Baseline	599	5 (< 1)	604	7 (1)

Note: Unless otherwise specified, all laboratory assessments after initiation of study medication, including post-medication follow-up were considered.

PCS = potentially clinically significant; TLV = telavancin; VAN = vancomycin; BUN = blood urea nitrogen.

[a] The total number of patients for each parameter represent the number of patients for the treatment group who (1) had that parameter assessed at baseline and at least one follow-up time and (2) for whom the baseline value was not elevated.

[b] Patients who had at least one abnormal value who met the criteria in footnote d.

Among patients with abnormal renal function at baseline, a total of 27 of 117 (23%) patients treated with telavancin and 14 of 119 (12%) patients treated with vancomycin developed a PCS change in serum creatinine. Abnormal renal function for this analysis was defined as a

serum creatinine value that was above the upper limit of normal and/or calculated CrCL ≤ 80 mL/min. Overall, 16% of patients treated with telavancin and 10% of patients treated with vancomycin experienced a PCS change in serum creatinine.

4.6.8.1.5 Impact of Risk Factors

In this severely ill NP patient population, a large number of underlying risk factors for renal dysfunction at baseline was to be expected. The following conditions were identified as potential risk factors: HIV disease, atheroembolic disease, heart failure, renal disease, liver disease, prostate disease, blood pressure abnormalities, cutaneous lupus erythematosus, dehydration, diabetes, multiple myeloma, potential urinary tract obstruction, rhabdomyolysis, sepsis, sickle cell anaemia, and systemic lupus erythematosus.

An analysis was performed to determine the frequency of renal AEs in patients with and without renal risk factors (as listed above) at baseline. As indicated in Table 39, data from the Phase 3 NP studies indicated that the risk of developing renal AEs in patients without comorbid conditions was small and similar between treatment groups: 2 of 141 patients (1%) in the telavancin group and 5 of 142 patients (4%) in the vancomycin group. In contrast, among patients with at least one baseline renal risk factor, approximately 12% of patients in the telavancin group and 9% of patients in the vancomycin group had a renal AE.

The incidence of renal SAEs was also examined based on the presence of risk factors (Table 39). Within the telavancin group, 0 of 141 patients with no renal risk factors had a renal SAE compared with 26 of 610 patients (4%) with a renal risk factor. The incidence of renal SAEs within the vancomycin group was similar regardless of the presence or absence of renal risk factors (2% and 3%, respectively).

Table 39: Renal AEs by Baseline Renal Risk Factors – Safety Population, Aggregated Studies 0015 and 0019

	Total for Studies 0015 & 0019	
	TLV (N = 751)	**VAN[a] (N = 752)**
Any Renal AE[b]	74 / 751 (10%)	57 / 752 (8%)
No Baseline Renal Risk Factors	2 / 141 (1%)	5 / 142 (4%)
Any Baseline Renal Risk Factor	72 / 610 (12%)	52 / 610 (9%)
At Least One Renal SAE [b]	26 / 751 (3%)	16 / 752 (2%)
No Baseline Renal Risk Factors	0 / 141 (0%)	4 / 142 (3%)
Any Baseline Renal Risk Factor	26 / 610 (4%)	12 / 610 (2%)

AE = adverse event; SAE = serious adverse event; TLV = telavancin; VAN = vancomycin.

[a] Includes 19 patients who received an antistaphylococcal penicillin instead of vancomycin.

[b] Includes the following preferred terms: renal failure acute, renal failure chronic, renal insufficiency, renal impairment, blood creatinine increased.

An analysis of the frequencies of renal function test PCS abnormalities in patients with and without renal risk factors at baseline was performed (Table 40). In patients without at least one baseline renal risk factor, the incidence of PCS abnormalities was similar between the two treatment groups. In patients with abnormal baseline renal function and any baseline renal risk factor, a higher incidence of PCS increases postbaseline in the telavancin group compared with the vancomycin group was again observed (27 of 115 patients [23%] vs 14 of 117 patients [12%]).

The current approved product label contains the following precautionary language:

(Renal) AEs were more likely to occur in patients with baseline comorbidities known to predispose patients to kidney dysfunction (pre-existing renal disease, diabetes mellitus, congestive heart failure, or hypertension). The renal AE rate was also higher in patients who received concomitant medications known to affect kidney function (eg, non-steroidal anti-inflammatory drugs, ACE inhibitors, and loop diuretics).

Table 40: PCS Abnormalities in Serum Creatinine by Baseline Renal Risk Factors – Safety Population, Studies 0015 and 0019

	0015		0019		Total	
	TLV (N = 372)	VAN[a] (N = 374)	TLV (N = 379)	VAN[b] (N = 378)	TLV (N = 751)	VAN[c] (N = 752)
No. of Patients with Normal Baseline[d]						
Patients with Any Baseline Renal Risk Factor[e]	221	242	243	225	464	467
Patients with No Baseline Renal Risk Factor	60	54	75	83	135	137
No. of Patients with Abnormal Baseline[f]						
Patients with Any Baseline Renal Risk Factor[e]	72	65	43	52	115	117
No. (%) of Patients with Normal Baseline Creatinine and a PCS Creatinine Increase[g]						
Patients with Any Baseline Renal Risk Factor[e]	40 (18%)	21 (9%)	35 (14%)	22 (10%)	75 (16%)	43 (9%)
Patients with No Baseline Renal Risk Factor	5 (8%)	5 (9%)	4 (5%)	7 (8%)	9 (7%)	12 (9%)
No. (%) of Patients with Abnormal Baseline Creatinine and a PCS Creatinine Increase[g]						
Patients with Any Baseline Renal Risk Factor[e]	18 (25%)	10 (15%)	9 (21%)	4 (8%)	27 (23%)	14 (12%)

PCS = potentially clinically significant; TLV = telavancin; VAN = vancomycin.

[a] Includes 9 patients who received an antistaphylococcal penicillin instead of vancomycin.

[b] Includes 11 patients who received an antistaphylococcal penicillin instead of vancomycin.

[c] Includes 20 patients who received an antistaphylococcal penicillin instead of vancomycin.

[d] Includes patients who had a normal serum creatinine result at baseline and at least one postbaseline result.

[e] Includes the following baseline renal risk factors: HIV, atheroembolic disease, heart failure, renal disease, liver disease, prostate disease, blood pressure abnormalities, cutaneous lupus erythematosus, dehydration, diabetes, multiple myeloma, potential obstruction, rhabdomyolysis, sepsis, sickle cell anaemia, and systemic lupus erythematosus.

[f] Includes patients who had a high serum creatinine result at baseline and at least one postbaseline result.

[g] Defined as any postbaseline creatinine ≥ 133 µmoL/L and at least 50% greater than baseline.

4.6.8.1.6 Effect of Concomitant Medications Known to Affect Renal Function

The NP efficacy and safety clinical database was reviewed for use of concomitant medications known to affect renal function (referred to as “renal concomitant medication”). In the aggregate Safety Population, 72% of patients treated with telavancin and 73% of patients treated with vancomycin received at least one renal concomitant medication, with approximately half of the patients in each treatment group having received furosemide concomitantly. Other common medications included vancomycin, captopril, enalapril, amikacin, and ibuprofen.

The receipt of such medication and incidence of renal AEs was explored, focusing on renal concomitant medications taken before the renal AE (Table 41). In the telavancin group, 66 patients (12%) taking a nephrotoxic concomitant medication had at least one renal AE compared with 55 patients (10%) in the vancomycin group. Of those patients who experienced a renal AE, the majority of patients in both treatment groups were taking a

nephrotoxic concomitant medication before the renal AE: 52 of 66 (79%) of patients in the telavancin group and 44 of 55 (80%) of patients in the vancomycin group. Eight patients in the telavancin group and 2 patients in the vancomycin group were not taking a nephrotoxic concomitant medication when they experienced a renal AE. Of the 8 telavancin-treated patients, 3 patients experienced an increase in blood creatinine, 3 patients experienced renal insufficiency, 1 patient experienced renal impairment, and 1 patient experienced acute renal failure.

Table 41: Renal AEs by Prior Renal Concomitant Medication – Safety Population, Studies 0015 and 0019

	0015		0019		Total	
	TLV (N = 372)	VAN[a] (N = 374)	TLV (N = 379)	VAN[b] (N = 378)	TLV (N = 751)	VAN[c] (N = 752)
Taking Renal Con Med[d] at Any Time	271 (73%)	280 (75%)	272 (72%)	267 (71%)	543 (72%)	547 (73%)
Had Renal AE[e]	34 (13%)	27 (10%)	32 (12%)	28 (10%)	66 (12%)	55 (10%)
Taking Renal Con Med [d] Prior to First Renal AE	24 (71%)	20 (74%)	28 (88%)	24 (86%)	52 (79%)	44 (80%)
Had No Renal AE	237 (87%)	253 (90%)	240 (88%)	239 (90%)	477 (88%)	492 (90%)
Not Taking Renal Con Med at Any Time	101 (27%)	94 (25%)	107 (28%)	111 (29%)	208 (28%)	205 (27%)
Had Renal AE[e]	3 (3%)	1 (1%)	5 (5%)	1 (< 1%)	8 (4%)	2 (< 1%)
Had No Renal AE	98 (97%)	93 (99%)	102 (95%)	110 (99%)	200 (96%)	203 (99%)

AE = adverse event; TLV = telavancin; VAN = vancomycin.

[a] Includes 9 patients who received an antistaphylococcal penicillin instead of vancomycin.

[b] Includes 11 patients who received an antistaphylococcal penicillin instead of vancomycin.

[c] Includes 20 patients who received an antistaphylococcal penicillin instead of vancomycin.

[d] Includes the following medications: ace inhibitor nos, aceclofenac, aciclovir, aciclovir sodium, adefovir dipivoxil, amikacin, amphotericin b, amphotericine b, liposome, benazepril, benazepril hydrochloride, captopril, carboplatin, celecoxib, cilazapril, colistin, cyclophosphamide, diclofenac, diclofenac potassium, diclofenac sodium, diclofenac w/misoprostol, enalapril, enalapril maleate, enalaprilat, fosinopril, fosinopril sodium, furosemide, furosemide sodium, gentamicin, ibuprofen, indinavir, indinavir sulfate, indometacin, indometacin sodium, interferons, ketoprofen, ketorolac, ketorolac tromethamine, ketotifen, lenograstim, lisinopril, lisinopril dihydrate, lornoxicam, mefenamic acid, meloxicam, methotrexate, meticillin, naproxen, naproxen sodium, netilmicin, parecoxib, parecoxib sodium, perindopril, perindopril erbumine, pipemidic acid, piroxicam, polymyxin b, quinapril, quinapril hydrochloride, ramipril, ritonavir, sirolimus, streptomycin, sulindac, tacrolimus, teicoplanin, tenofovir, tenofovir disoproxil fumarate, tobramycin, trandolapril, valdecoxib, vancomycin, zofenopril.

[e] Includes the following preferred terms: renal failure acute, renal failure chronic, renal insufficiency, renal impairment, blood creatinine increased.

4.6.8.2 Cardiac Safety and QTc Prolongation Effects

In nonclinical studies, in vivo assays failed to detect an effect on cardiac repolarization; however, the observation of effects in two of the in vitro studies (hERG and canine Purkinje

fiber) suggested that a prolongation of the QTc interval in humans may be possible (Section 4.1.2). In the Phase 1 ECG study, the time-averaged primary analysis showed that telavancin administered at 7.5 mg/kg and 15 mg/kg resulted in less than a 5 msec prolongation of QTcF (with no evident dose response) in comparison with placebo and a significantly reduced compared with the 9.2 msec effect of the positive control, moxifloxacin. These results indicated that at the doses of telavancin studied, and by interpolation, at doses in between, treatment with telavancin should result in minimal, if any, risk of torsades de pointes.

4.6.8.2.1 Review of Cardiac Adverse Events

In the aggregated NP Safety Population, the incidence of cardiac AEs was 17% for the telavancin group and 19% for the vancomycin group. A total of 16 patients (11 treated with telavancin and 5 treated with vancomycin) experienced an AE of ECG QTc interval prolonged or ECG QT prolonged; none of these events were reported as an SAE.

4.6.8.2.2 Cardiac Deaths

Sixteen (2%) patients treated with telavancin and 32 (4%) patients treated with vancomycin died after experiencing a cardiac AE. None of the deaths was reported as the outcome of a AE of QTc interval prolongation. The number of patients in the telavancin group who died of a cardiac SAE were as follows: cardiac failure congestive (3 patients), bradycardia (2 patients), cardiac arrest (2 patients), 1 patient had both a myocardial infarction and ventricular fibrillation that resulted in death, and 1 patient each had acute coronary syndrome, atrioventricular block complete, cardiac failure, cardiac failure acute, cardio-respiratory arrest, cardiogenic shock, ischemic cardiomyopathy, or myocardial ischemia.

The cardiac SAEs with an outcome of death in the vancomycin group were: cardiac failure congestive (8 patients), cardiac failure (5 patients), cardiac arrest (3 patients), acute myocardial infarction (2 patients), bradycardia (2 patients), ventricular fibrillation (2 patients), ventricular tachycardia (2 patients), and 1 patient each had acute coronary syndrome, atrial fibrillation, cardiogenic shock, cardiopulmonary failure, cardiovascular disorder, coronary artery disease, left ventricular failure, myocardial infarction, and myocardial ischemia. One of the 32 patients had 2 fatal cardiac SAEs (ventricular fibrillation and ventricular tachycardia). No deaths due to cardiac events in patients treated with vancomycin were considered possibly/probably related to study drug. One vancomycin patient experienced “sudden cardiac death” that was not captured under the cardiac SOC owing to coding.

4.6.8.2.3 Electrocardiograms

In the Phase 3 NP studies, 12-lead ECGs were obtained in triplicate before the initial dose of study medication; after infusion on Study Days 4, 7, 10, 14, 17, and 21; and at the EOT Visit.

A summary of outlier values of QTcF for the Safety Population of the NP studies is presented in Table 42. Data presented in this and all other tabular summaries were derived from central laboratory manually read ECGs.

The incidence of QTcF outliers (change from baseline > 60 msec or postbaseline value > 500 msec) was similar between treatment groups of the aggregated NP Safety Population (Table 42).

Table 42: Incidence of QTcF Outliers – Safety Population, Aggregated Studies 0015 and 0019

	TLV[a] (N = 631)	VAN[a] (N = 641)
Number (%) of Patients		
Max Change from Baseline > 60 msec	48 (7.6%)	44 (6.9%)
Max Postbaseline Value > 500 msec	12 (1.9%)	12 (1.9%)
Either Max Change > 60 msec or Max Postbaseline Value > 500 msec	52 (8.2%)	48 (7.5%)
Both > 60 msec Change and Max Postbaseline Value > 500 msec	8 (1.3%)	8 (1.2%)

QTcF = corrected QT interval using Fridericia's correction; TLV = telavancin; VAN = vancomycin.
[a] The denominator for the percentages was comprised of those patients who experienced a QTcF outlier or patients who had both a baseline QTcF result and at least one postbaseline result.

In the aggregated Safety Population, 52 (7%) patients treated with telavancin and 48 (6%) patients treated with vancomycin met criteria for either a maximum change > 60 msec or a maximum postbaseline value > 500 msec. Within this subset of patients with outlying QTc values, a higher proportion of patients experienced cardiac AEs in the vancomycin group (35%) compared with the telavancin group (17%).

4.6.9 On-Treatment Reductions in Renal Function and Risk for Mortality

Given the proposed labeling to warn against the use of telavancin in patients with pre-existing severe renal impairment, an important issue to address is whether patients with baseline CrCL ≥ 30 mL/min are at increased risk for mortality if, during treatment with telavancin, their renal function deteriorates. This was examined using creatinine values obtained during study treatment. Table 43 displays the mortality (survival) rates for patients with CrCL ≥ 30 mL/min who experienced a decrease in estimated creatinine clearance < 30 mL/min at any time during treatment.

For the patients who experienced a decline of at least 5 mL/min in CrCL to less than 30 mL/min during therapy, there was an increased risk for mortality in both treatment groups, but higher in patients treated with telavancin. However, if the decline in CrCL did not reach this threshold, mortality was similar.

Table 43: All-Cause, 28-Day Survival Differences by On-Treatment Decrease in CrCL – AT Population with CrCL ≥ 30 mL/min, Aggregated Studies 0015 and 0019

	Patients, Mortality (Survival) (%)		
	TLV	VAN	Difference (95% CI)
Any Decrease < 30 mL/min[a] (n = 94)	31 (49.7%)	12 (61.0%)	-11.3 (-32.6, 10.0)
No Decrease < 30 mL/min (n = 113)	79 (85.7%)	99 (83.1%)	2.6 (-1.7, 6.9)

[a] At least 5 mL/min decrease.
CrCL = creatinine clearance; AT = all-treated; CI = confidence interval; TLV = telavancin; VAN = vancomycin.

Further exploration of this finding was carried out in the population of patients most likely to benefit from treatment, those with only Gram-positive infections. Table 44 displays the findings when these patients experience a decline of at least 5 mL/min in renal function to < 30 mL/min during treatment. Here in contrast, there was no increase in risk (with very few deaths), and again, patients without such a decline also have no increased risk. These data provide further support for the safety of telavancin in the treatment of Gram-positive NP.

Table 44: All-Cause, 28-Day Survival Differences by On-Treatment Decrease in CrCL – MPP Population with CrCL ≥ 30 mL/min, Aggregated Studies 0015 and 0019

	Patients, Mortality (Survival) (%)		
	TLV	VAN	Difference (95% CI)
Any Decrease < 30 mL/min[a] (n = 32)	9 (55.0%)	5 (55.6%)	-0.6 (-37.0, 35.8)
No Decrease < 30 mL/min (n = 418)	36 (83.1%)	37 (81.1%)	2.0 (-5.5, 9.5)

[a] At least 5 mL/min decrease.
CrCL = creatinine clearance; MPP = modified per-protocol; CI = confidence interval; TLV = telavancin; VAN = vancomycin.

Patients treated with telavancin should have their renal function monitored carefully, and if renal function declines significantly during treatment, appropriate dosage adjustments should be made, consideration should be given to continuing telavancin if the anticipated benefit to the patient outweighs the potential risk, or discontinuation if other appropriate options for treatment are available.

4.6.10 Safety in Pregnancy

In nonclinical developmental studies there were minor fetal effects, including lower fetal weights in rats and a low incidence of limb defects. Because there are no adequate and well-controlled studies in pregnant women, telavancin should be used during pregnancy only if the potential benefit to the patient outweighs potential risk to the fetus.

4.6.11 Postmarketing Safety

Since approval in September of 2009, it is estimated that approximately 125,000 patients have been exposed to at least one dose of telavancin. Table 45 displays a summary of the spontaneous reports of AEs reported to Theravance from approval to the present time. The

types of AEs reported are consistent with those from the clinical studies and no new unexpected events have been reported. A total of 8 deaths have been reported due to a variety of causes. One of the deaths was in a patient treated for NP, who had numerous complex underlying conditions, including acute renal failure, and died from cavitary pneumonia (of unknown etiology) and MOF despite treatment with telavancin.

Table 45: Summary of Spontaneous Reports of AEs Reported to the Sponsor since Approval

AE	n
Nausea	30
Blood Creatinine Increased	20
Rash	20
Dysgeusia	17
Renal Failure Acute	17
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AE = adverse event; INR = international normalized ratio.

4.6.12 Safety Conclusions

Overall, rates of adverse reactions in patients treated with telavancin were comparable to those for vancomycin. There were slightly higher rates of SAEs and discontinuations due to AEs in the patients treated with telavancin compared with vancomycin. The differences in SAEs of MOF and sepsis/septic shock could be attributed to a lower rate of administering adequate Gram-negative coverage in the telavancin group.

Rates of increases in serum creatinine (to 1.5-fold baseline values) were higher in patients who received telavancin. There were similar proportions of renal AEs in each group that resolved or improved during the course of follow-up. There were no observed differences in QTc interval outliers among patients treated with either telavancin or vancomycin and no

evident cardiac AEs associated with QT prolongation, although the rate of cardiac AEs was higher among vancomycin-treated patients who had outlier QTc values during study.

A mortality risk was observed for telavancin in patients with a baseline CrCL < 30 mL/min compared with vancomycin-treated patients. Further, mortality risk was observed for patients with baseline CrCL > 30 mL/min and whose CrCL decreased below 30 mL/min while on treatment with telavancin. For patients with CrCL > 30 mL/min and no decrease below 30 mL/min on treatment, survival in both groups was similar. The mortality risk appeared to be confined to patients other than those who only had Gram-positive pathogens recovered from baseline cultures.

Theravance conducted intensive and comprehensive exploratory modeling using Cox proportional hazards models, logistic regression models, and decision trees to describe the variation in the current study population for factors that were explanatory for the all-cause mortality outcome. Multiple factors associated with renal function were consistently identified across all models as having significant treatment interactions, with CrCL being of primary significance. Decision trees determined an optimal threshold of CrCL < 33 mL/min for association with increased mortality risk. As this was very close to a dose adjustment threshold of CrCL < 30 mL/min, which is used for many drugs, it was believed that using CrCL < 30 mL/min represents an acceptable balance of statistical modeling and clinical utility.

There is no ready explanation for an association between telavancin and higher mortality rates in patients with baseline severe renal impairment. Although it is tempting to postulate a relationship between the nephrotoxicity associated with use of telavancin and the risk for increased mortality in patients with baseline severe renal impairment, no clear link has been established after examining the case histories for these patients. There are data suggesting an excess of deaths due to Gram-negative infections. In an abundance of caution and concern for patient safety, the proposed labeling warns against the use of telavancin in patients with baseline severe renal impairment unless the anticipated benefit outweighs the potential risk.

Therefore, patients should have their renal function monitored carefully, appropriate dosage adjustments made if renal function declines, consideration should be given to continuing telavancin if the anticipated benefit to the patient outweighs the potential risk, or discontinuation if other appropriate options for treatment are available.

5 RISK EVALUATION AND MITIGATION STRATEGY (REMS)

An informational program for healthcare providers (HCPs) and patients has been established to help minimize the risks associated with the use of telavancin including the risk for developmental toxicity. Animal data indicate that use of telavancin during pregnancy is associated with reduced fetal weights and increased rates of digit and limb malformations in offspring, although these malformations were infrequent. Elements of the REMS program include a Medication Guide, which is distributed to each patient receiving telavancin treatment, and a Communication Plan to educate HCPs on the potential risk of fetal development toxicity. To date, more than 1.3 million Dear HCP letters have been distributed to targeted HCPs.

Proposed modifications to the REMS program include revision of the Medication Guide to include a description of the mortality risk in patients with severe renal impairment at baseline. The REMS Communication Plan will be expanded to include a goal of ensuring each prescribing clinician is cognizant of the differential outcome in patients with baseline severe renal impairment.

6 STUDY CONDUCT – QUALITY ASSURANCE

Theravance retained contract research organizations to monitor the investigative sites on a periodic basis. All patient data were verified against source documents and site procedures were reviewed for compliance with applicable local, state and federal regulations, including those related to human subjects' protections. Theravance also audited the conduct and monitoring of these studies, confirming that the investigative sites, contract research organizations, and central laboratories complied with Good Clinical Practice. Additionally, key eligibility criteria and determination of clinical response at 113 investigative sites, covering approximately 76% of the enrolled patients, were reviewed again after study closure to further verify the integrity of clinical site data documentation.

7 BENEFIT/RISK AND CONCLUSIONS

There is a need for new antibiotics that will effectively treat resistant Gram-positive bacterial strains and that have a low potential for development of resistance. Telavancin exerts potent bactericidal activity through a mechanism that combines inhibition of cell wall synthesis and disruption of bacterial membrane function. MICs for telavancin are lower than glycopeptide comparators (vancomycin and teicoplanin). Organisms resistant to other classes of antibiotics, including oxacillin, daptomycin, and linezolid, remain susceptible to telavancin at the proposed MIC breakpoints. Bacterial resistance to telavancin has not been detected in either in vitro or clinical studies.

Telavancin is an effective antibiotic for the treatment of NP due to Gram-positive pathogens, including MRSA. Importantly, no telavancin resistance has been observed in the clinic. In 2, adequate and well-controlled clinical trials, telavancin has been shown to be an effective treatment of NP due to Gram-positive pathogens with demonstrated noninferiority to vancomycin based on the prespecified clinical response at TOC endpoint, as well as a post-hoc secondary all-cause mortality endpoint (lower bound of the 95% CI greater than −10% for both endpoints). Moreover, higher cure rates and survival rates were observed in patients with only Gram-positive pathogens recovered from baseline cultures.

Higher cure rates were also observed in telavancin-treated patients whose baseline *S. aureus* had higher MICs to vancomycin (≥ 1 µg/mL), as well as in a small group of patients found to be infected with hVISA. Higher cure rates in the telavancin group were observed in patients considered to be at risk for poor outcomes (elderly, bacteremic, and with high APACHE II scores). Patients with VAP treated with telavancin also experienced higher cure rates than those treated with vancomycin.

Higher mortality rates were seen in both treatment groups among patients with baseline severe renal impairment (CrCL < 30 mL/min). However, the mortality rates for the telavancin group were higher. Given this finding, it is recommended to limit the use of telavancin in the treatment of NP to patients with CrCL ≥ 30 mL/min, and that patients with baseline severe renal impairment should only receive telavancin if the anticipated benefit to the patient outweighs the potential risk. If renal function deteriorates significantly during the course of treatment, appropriate dosage adjustments should be made, consideration given to continuing telavancin if the anticipated benefit to the patient outweighs the potential risk (eg, no other viable options), or discontinuing telavancin and using a suitable alternate agent.

Overall, the safety profile of telavancin is well-characterized. The overall incidence of AEs was the same in both treatment groups, but the rates of SAEs and AEs leading to drug discontinuation were slightly higher in the telavancin group. Higher rates of MOF and sepsis/septic shock were observed in the telavancin group, but appeared to be due to higher rates of inadequate Gram-negative antibiotic coverage in the telavancin group. If appropriate Gram-negative coverage was given, the rates of these AEs were similar.

The incidence of renal AEs was slightly higher in the telavancin group (10% vs 8%), but in patients without risk factors for renal impairment, the renal event rates were slightly lower in the telavancin group. Increases in creatinine to 1.5-fold baseline were higher in the telavancin group. Resolution of renal events was similar in both treatment groups. As noted above, serum creatinine should be carefully monitored in patients receiving telavancin, with consideration given to dosage reduction or discontinuation of the drug if renal function worsens significantly during treatment.

Overall, telavancin has been shown to be an effective treatment for NP due to Gram-positive pathogens, when prescribed and monitored according to the proposed labeling.

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9 APPENDICES

Appendix 1: Criteria Used to Determine Clinical Evaluability

To have been deemed to have adhered to protocol expectations, and on that basis to have been included in the CE Population, a patient must have met the following criteria:

- Patient met the following protocol inclusion criteria, or else was approved for enrollment by the Study Hotline Monitor:
    - Inclusion criterion 2, which required certain signs and symptoms consistent with pneumonia
    - Inclusion criterion 3, which required a chest radiograph consistent with a diagnosis of pneumonia
    - Inclusion criterion 4, which required the availability of appropriate specimens for Gram stain and culture and venous access for dosing
- Patient did not violate the following protocol exclusion criteria, or else was approved for enrollment by the study hotline monitor:
    - Exclusion criterion 1, which excluded patients who had received more than a specified amount of potentially effective systemic antibiotic therapy for Gram-positive pneumonia immediately prior to randomization
    - Exclusion criterion 2, which excluded patients with respiratory tract specimens or sputum with only Gram-negative bacteria
    - Exclusion criterion 3, which excluded patients with MSSA or *S. pneumoniae* who also required more than a specified amount of concomitant antibiotic therapy for Gram-negative coverage that had activity versus MSSA or *S. pneumoniae*
    - Exclusion criterion 4, which excluded patients with known or suspected pulmonary disease that precluded evaluation of therapeutic response, cystic fibrosis, or active tuberculosis
    - Exclusion criterion 5, which excluded patients with known or suspected *Legionella pneumophila* pneumonia
    - Exclusion criterion 6, which excluded patients who were known or suspected to be infected with an organism that is not susceptible to medications permitted by the protocol
    - Exclusion criterion 7, which excluded patients with documented or suspected meningitis, endocarditis, or osteomyelitis
- The patient's identified analysis pathogen(s) were not solely Gram-negative pathogens. That is, either the patient had a Gram-positive analysis pathogen, or no analysis pathogen was identified.
- The patient did not have pneumonia due to *Stenotrophomonas maltophilia* or *Burkholderia cepacia* at Baseline.
- The patient did not have a persistent *S. aureus* bacteremia, defined as two or more *S. aureus*-positive blood cultures on different days between Study Day 1 and TOC, inclusive.

- The patient did not receive more than 2 days of vancomycin or teicoplanin between Study Day -4 and Study Day 1, inclusive. The rationale for excluding patients who had received prior treatment with vancomycin was to exclude prior treatment failures to vancomycin. Only IV vancomycin was to be considered as a potential basis for exclusion from the CE Population; oral administration was not to be a basis for exclusion.
- The patient was treated with the study medication assigned by the randomization.
- The patient received at least 80% of intended doses of active study medication.
- The patient did not receive PEA therapy for more than 2 calendar days any time before the TOC assessment. The day of the TOC assessment was not counted for this criterion.
- The patient was a failure at EOT, or else was either a cure or a failure at TOC.
- If the patient was not a failure at EOT, then the TOC assessment was made between Study Day 6P (ie, 6 days after EOT) and Study Day 28P, inclusive.
- If the patient was a cure, the patient received at least 5 days of active study medication.
- If the patient was a failure, the patient received active study medication daily through Study Day 3.

Additionally, for patients who died on or after Study Day 3, where the death was attributable to the NP episode under study, the receipt of PEA therapy was not to exclude them from the CE Population.

Appendix 2: Prescribing Information for Telavancin, cSSSI

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VIBATIV safely and effectively. See full prescribing information for VIBATIV.

VIBATIV (telavancin) for injection, for intravenous use
Initial U.S. Approval: 2009

To reduce the development of drug-resistant bacteria and maintain the effectiveness of VIBATIV and other antibacterial drugs, VIBATIV should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

WARNING: FETAL RISK
See full prescribing information for complete boxed warning.

- **Women of childbearing potential should have a serum pregnancy test prior to administration of VIBATIV. (8.1)**
- **Avoid use of VIBATIV during pregnancy unless potential benefit to the patient outweighs potential risk to the fetus. (8.1)**
- **Adverse developmental outcomes observed in 3 animal species at clinically relevant doses raise concerns about potential adverse developmental outcomes in humans. (8.1)**

----------INDICATIONS AND USAGE----------

VIBATIV is a lipoglycopeptide antibacterial indicated for the treatment of adult patients with complicated skin and skin structure infections (cSSSI) caused by susceptible Gram-positive bacteria. (1.1)

----------DOSAGE AND ADMINISTRATION----------

- 10 mg/kg administered over 60 minutes by intravenous infusion once every 24 hours for 7 to 14 days. (2.1)
- Dosage adjustment in patients with renal impairment. (2.2):

Creatinine Clearance[#] (mL/min)	VIBATIV Dosage Regimen
>50	10 mg/kg every 24 hours
30-50	7.5 mg/kg every 24 hours
10- <30	10 mg/kg every 48 hours

[#] As calculated using the Cockcroft-Gault formula (12.3)

----------DOSAGE FORMS AND STRENGTHS ----------

Single-use vials containing either 250 or 750 mg telavancin. (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Nephrotoxicity: New onset or worsening renal impairment has occurred. Monitor renal function in all patients. (5.3)
- Decreased efficacy with moderate/severe baseline renal impairment: Consider these data when selecting antibacterial therapy for patients with baseline CrCl ≤50 mL/min. (5.4)
- Infusion-related reactions: Administer VIBATIV over at least 60 minutes to minimize infusion-related reactions. (5.5)
- *Clostridium difficile*-associated disease: May range from mild diarrhea to fatal colitis. Evaluate if diarrhea occurs. (5.6)
- QTc prolongation: Avoid use in patients at risk. Use with caution in patients taking drugs known to prolong the QT interval. (5.8)
- Coagulation test interference: Telavancin interferes with some laboratory coagulation tests, including prothrombin time, international normalized ratio, and activated partial thromboplastin time. (5.9, 7.1)

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥10% of patients treated with VIBATIV) include: taste disturbance, nausea, vomiting, and foamy urine. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Medical Information at 1-800-727-7003 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based on animal data, may cause fetal harm. Pregnancy registry available. (8.1)
- Pediatric patients: Safety and efficacy not demonstrated. (8.4)

See 17 for PATIENT COUNSELING INFORMATION AND MEDICATION GUIDE

Revised: 01/2012

FULL PRESCRIBING INFORMATION: CONTENTS

FULL PRESCRIBING INFORMATION

WARNING: FETAL RISK

- **Women of childbearing potential should have a serum pregnancy test prior to administration of VIBATIV**
- **Avoid use of VIBATIV during pregnancy unless the potential benefit to the patient outweighs the potential risk to the fetus**
- **Adverse developmental outcomes observed in 3 animal species at clinically relevant doses raise concerns about potential adverse developmental outcomes in humans *[see Warnings and Precautions (5.1), Use in Specific Populations (8.1)]***

1 INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of VIBATIV and other antibacterial drugs, VIBATIV should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

1.1 Complicated Skin and Skin Structure Infections

VIBATIV is indicated for the treatment of adult patients with complicated skin and skin structure infections (cSSSI) caused by susceptible isolates of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group (includes *S. anginosus, S. intermedius,* and *S. constellatus)*, or *Enterococcus faecalis* (vancomycin-susceptible isolates only).

Combination therapy may be clinically indicated if the documented or presumed pathogens include Gram-negative organisms.

Appropriate specimens for bacteriological examination should be obtained in order to isolate and identify the causative pathogens and to determine their susceptibility to telavancin. VIBATIV may be initiated as empiric therapy before results of these tests are known.

2 DOSAGE AND ADMINISTRATION

2.1 Complicated Skin and Skin Structure Infections

The recommended dosing for VIBATIV is 10 mg/kg administered over a 60-minute period in patients ≥18 years of age by intravenous infusion once every 24 hours for 7 to 14 days. The duration of therapy should be guided by the severity and site of the infection and the patient's clinical and bacteriological progress.

2.2 Patients with Renal Impairment

Because telavancin is eliminated primarily by the kidney, a dosage adjustment is required for patients whose creatinine clearance is ≤50 mL/min, as listed in Table 1 *[see Clinical Pharmacology (12.3)]*.

Table 1: Dosage Adjustment in Adult Patients with Renal Impairment

Creatinine Clearance* (mL/min)	**VIBATIV Dosage Regimen**
>50	10 mg/kg every 24 hours
30 - 50	7.5 mg/kg every 24 hours
10 - <30	10 mg/kg every 48 hours

* As calculated using the Cockcroft-Gault formula [see *Clinical Pharmacology (12.3)*]

There is insufficient information to make specific dosage adjustment recommendations for patients with end-stage renal disease (CrCl <10 mL/min), including patients undergoing hemodialysis.

2.3 Preparation and Administration

250 mg vial: Reconstitute the contents of a VIBATIV 250 mg vial with **15** mL of 5% Dextrose Injection, USP; Sterile Water for Injection, USP; or 0.9% Sodium Chloride Injection, USP. The resultant solution has a concentration of 15 mg/mL (total volume of approximately 17.0 mL).

750 mg vial: Reconstitute the contents of a VIBATIV 750 mg vial with **45** mL of 5% Dextrose Injection, USP; Sterile Water for Injection, USP; or 0.9% Sodium Chloride Injection, USP, The resultant solution has a concentration of 15 mg/mL (total volume of approximately 50.0 mL).

The following formula can be used to calculate the volume of reconstituted VIBATIV solution required to prepare a dose:

Telavancin dose (mg) = 10 mg/kg or 7.5 mg/kg x patient weight (in kg) (see Table 1)

$$\textbf{Volume of reconstituted solution (mL)} = \frac{\textbf{Telavancin dose (mg)}}{\textbf{15 mg/mL}}$$

For doses of 150 to 800 mg, the appropriate volume of reconstituted solution must be further diluted in 100 to 250 mL prior to infusion. Doses less than 150 mg or greater than 800 mg should be further diluted in a volume resulting in a final concentration of 0.6 to 8 mg/mL. Appropriate infusion solutions include: 5% Dextrose Injection, USP; 0.9% Sodium Chloride Injection, USP; or Lactated Ringer's Injection, USP. The dosing solution should be administered by intravenous infusion over a period of 60 minutes.

Reconstitution time is generally under 2 minutes, but can sometimes take up to 20 minutes. Mix thoroughly to reconstitute and check to see if the contents have dissolved completely. Parenteral drug products should be inspected visually for particulate matter prior to administration. Discard the vial if the vacuum did not pull the diluent into the vial.

Since no preservative or bacteriostatic agent is present in this product, aseptic technique must be used in preparing the final intravenous solution. Studies have shown that the reconstituted solution in the vial should be used within 4 hours when stored at room temperature or within 72 hours under refrigeration at 2 to 8°C (36 to 46°F). The diluted (dosing) solution in the infusion bag should be used within 4 hours when stored at room temperature or used within 72 hours when stored under refrigeration at 2 to 8°C (36 to 46°F). However, the total time in the vial plus the time in the infusion bag should not exceed 4 hours at room temperature and 72 hours under refrigeration at 2 to 8°C (36 to 46°F).

VIBATIV is administered intravenously. Because only limited data are available on the compatibility of VIBATIV with other IV substances, additives or other medications should not be added to VIBATIV single-use vials or infused simultaneously through the same IV line. If the same intravenous line is used for sequential infusion of additional medications, the line should be flushed before and after infusion of VIBATIV with 5% Dextrose Injection, USP; 0.9% Sodium Chloride Injection, USP; or Lactated Ringer's Injection, USP.

3 DOSAGE FORMS AND STRENGTHS

VIBATIV is supplied in single-use vials containing either 250 or 750 mg telavancin as a sterile, lyophilized powder.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Women of Childbearing Potential

Women of childbearing potential should have a serum pregnancy test prior to administration of VIBATIV. If not already pregnant, women of childbearing potential should use effective contraception during VIBATIV treatment.

5.2 Pregnancy

Avoid use of VIBATIV during pregnancy unless the potential benefit to the patient outweighs the potential risk to the fetus. VIBATIV caused adverse developmental outcomes in 3 animal species at clinically relevant doses. This raises concern about potential adverse developmental outcomes in humans *[see Use in Specific Populations (8.1)]*.

5.3 Nephrotoxicity

Increases in serum creatinine to 1.5 times baseline occurred more frequently among VIBATIV-treated patients with normal baseline serum creatinine (15%) compared with vancomycin-treated patients with normal baseline serum creatinine (7%).

In 30/929 (3.1%) of VIBATIV-treated patients compared to 10/938 (1.1%) of vancomycin-treated patients, renal adverse events indicative of renal impairment occurred, as defined by the following terms: increased serum creatinine, renal impairment, renal insufficiency, and/or renal failure. In 17 of the 30 VIBATIV-treated patients, these adverse events had not completely resolved by the end of the trials, compared with 6 of the 10 vancomycin-treated patients. Serious adverse events indicative of renal impairment occurred in 11/929 (1.2%) of VIBATIV-treated patients compared to 3/938 (0.3%) of vancomycin-treated patients. Twelve patients treated with VIBATIV discontinued treatment due to adverse events indicative of renal impairment compared to 2 patients treated with vancomycin. Adverse events were more likely to occur in patients with baseline comorbidities known to predispose patients to kidney dysfunction (pre-existing renal disease, diabetes mellitus, congestive heart failure, or hypertension). The renal adverse event rate was also higher in patients who received

concomitant medications known to affect kidney function (eg, non-steroidal anti-inflammatory drugs, ACE inhibitors, and loop diuretics). Fifteen of 174 patients (8.6%) ≥65 years of age had adverse events indicative of renal impairment compared to 16 of 755 patients (1.9%) <65 years of age *[see Use in Specific Populations (8.5)]*.

Monitor renal function (i.e., serum creatinine, creatinine clearance) in all patients receiving VIBATIV. Values should be obtained prior to initiation of treatment, during treatment (at 48- to 72-hour intervals or more frequently, if clinically indicated), and at the end of therapy. If renal function decreases, the benefit of continuing VIBATIV versus discontinuing and initiating therapy with an alternative agent should be assessed *[see Dosage and Administration, Clinical Pharmacology (2.2)]*.

In patients with renal dysfunction, accumulation of the solubilizer hydroxypropyl-beta-cyclodextrin can occur *[see Patients with Renal Impairment (8.6) and Clinical Pharmacology (12.3)]*.

5.4 Decreased Efficacy with Moderate/Severe Baseline Renal Impairment

In a subgroup analysis of the pooled cSSSI studies, clinical cure rates in the telavancin-treated patients were lower in patients with baseline CrCl ≤50 mL/min compared to those with CrCl >50 mL/min (Table 2). A decrease of this magnitude was not observed in vancomycin-treated patients. Consider these data when selecting antibacterial therapy for use in patients with baseline moderate/severe renal impairment.

Table 2: Clinical Cure by Baseline Renal Function

	VIBATIV % (n/N)	**Vancomycin % (n/N)**
ATe Population[1]		
CrCl >50 mL/min	75.3% (565/750)	73.7% (575/780)
CrCl ≤50 mL/min	63.1% (70/111)	69.4% (75/108)
CE Population[2]		
CrCl >50 mL/min	87.0% (520/598)	85.9% (524/610)
CrCl ≤50 mL/min	67.4% (58/86)	82.7% (67/81)

[1] All-treated population - includes all patients randomized, treated, and evaluated for efficacy
[2] Clinically evaluable population

5.5 Infusion-Related Reactions

VIBATIV is a lipoglycopeptide antibacterial agent and should be administered over a period of 60 minutes to reduce the risk of infusion-related reactions. Rapid intravenous infusions of

the glycopeptide class of antimicrobial agents can cause “Red-man Syndrome”-like reactions including: flushing of the upper body, urticaria, pruritus, or rash. Stopping or slowing the infusion may result in cessation of these reactions.

5.6 *Clostridium difficile*-Associated Diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported with nearly all antibacterial agents and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the flora of the colon and may permit overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hyper-toxin-producing strains of *C. difficile* cause increased morbidity and mortality, since these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary because CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

5.7 Development of Drug-Resistant Bacteria

Prescribing VIBATIV in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

As with other antibacterial drugs, use of VIBATIV may result in overgrowth of nonsusceptible organisms, including fungi. Patients should be carefully monitored during therapy. If superinfection occurs, appropriate measures should be taken.

5.8 QTc Prolongation

In a study involving healthy volunteers, doses of 7.5 and 15 mg/kg of VIBATIV prolonged the QTc interval *[see Clinical Pharmacology (12.2)]*. Caution is warranted when prescribing VIBATIV to patients taking drugs known to prolong the QT interval. Patients with congenital long QT syndrome, known prolongation of the QTc interval, uncompensated heart failure, or

severe left ventricular hypertrophy were not included in clinical trials of VIBATIV. Use of VIBATIV should be avoided in patients with these conditions.

5.9 Coagulation Test Interference

Although telavancin does not interfere with coagulation, it interfered with certain tests used to monitor coagulation (Table 3), when conducted using samples drawn 0 to 18 hours after VIBATIV administration for patients being treated once every 24 hours. Blood samples for these coagulation tests should be collected as close as possible prior to a patient's next dose of VIBATIV. Blood samples for coagulation tests unaffected by VIBATIV may be collected at any time *[see Drug Interactions (7.1)]*.

Table 3: Coagulation Tests Affected and Unaffected by Telavancin

Affected by Telavancin	Unaffected by Telavancin
Prothrombin time International normalized ratio Activated partial thromboplastin time Activated clotting time Coagulation based factor Xa tests	Thrombin time Whole blood (Lee-White) clotting time Ex vivo platelet aggregation Chromogenic factor Xa assay Functional (chromogenic) factor X assay Bleeding time D-dimer Fibrin degradation products

No evidence of increased bleeding risk has been observed in clinical trials with VIBATIV. Telavancin has no effect on platelet aggregation. Furthermore, no evidence of hypercoagulability has been seen, as healthy subjects receiving VIBATIV have normal levels of D-dimer and fibrin degradation products.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Nephrotoxicity *[see Warnings and Precautions (5.3)]*
- Infusion-related reactions *[see Warnings and Precautions (5.5)]*
- *Clostridium difficile*-associated diarrhea *[see Warnings and Precautions (5.6)]*

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trials Experience

The two Phase 3 cSSSI clinical trials (Trial 1 and Trial 2) for VIBATIV included 929 adult patients treated with VIBATIV at 10 mg/kg IV once daily. The mean age of patients treated with VIBATIV was 49 years (range 18-96). There was a slight male predominance (56%) in patients treated with VIBATIV, and patients were predominantly Caucasian (78%).

In the cSSSI clinical trials, <1% (8/929) patients who received VIBATIV died and <1% (8/938) patients treated with vancomycin died. Serious adverse events were reported in 7% (69/929) of patients treated with VIBATIV and most commonly included renal, respiratory, or cardiac events. Serious adverse events were reported in 5% (43/938) of vancomycin-treated patients, and most commonly included cardiac, respiratory, or infectious events. Treatment discontinuations due to adverse events occurred in 8% (72/929) of patients treated with VIBATIV, the most common events being nausea and rash (~1% each). Treatment discontinuations due to adverse events occurred in 6% (53/938) of vancomycin-treated patients, the most common events being rash and pruritus (~1% each).

The most common adverse reactions occurring in ≥10% of VIBATIV-treated patients observed in the VIBATIV Phase 3 cSSSI trials were taste disturbance, nausea, vomiting, and foamy urine.

Table 4 displays the incidence of treatment-emergent adverse drug reactions reported in >2% of patients treated with VIBATIV possibly related to the drug (including those reactions known to occur with other glycopeptide antibacterial agents).

Table 4: Incidence of Treatment-emergent Adverse Drug Reactions Reported in ≥2% of VIBATIV or Vancomycin Patients Treated in Trial 1 and Trial 2

	VIBATIV (N=929)	**Vancomycin (N=938)**
Body as a Whole		
Rigors	4%	2%
Generalized pruritus	3%	6%
Digestive System		

	VIBATIV (N=929)	Vancomycin (N=938)
Nausea	27%	15%
Vomiting	14%	7%
Diarrhea	7%	8%
Abdominal pain	2%	2%
Metabolic and Nutritional		
Decreased appetite	3%	2%
Nervous System		
Taste disturbance[1]	33%	7%
Dizziness	6%	6%
Renal System		
Foamy urine	13%	3%
Skin and Appendages		
Pruritus	6%	13%
Rash	4%	5%
Other		
Infusion site pain	4%	4%
Infusion site erythema	3%	3%

[1] Described as a metallic or soapy taste.

7 DRUG INTERACTIONS

7.1 Drug-Laboratory Test Interactions

Effects of Telavancin on Coagulation Test Parameters

Telavancin binds to the artificial phospholipid surfaces added to common anticoagulation tests, thereby interfering with the ability of the coagulation complexes to assemble on the surface of the phospholipids and promote clotting in vitro. These effects appear to depend on the type of reagents used in commercially available assays. Thus, when measured shortly after completion of an infusion of VIBATIV, increases in the PT, INR, aPTT, and ACT have been observed. These effects dissipate over time, as plasma concentrations of telavancin decrease.

Urine Protein Tests

Telavancin interferes with urine qualitative dipstick protein assays, as well as quantitative dye methods (e.g., pyrogallol red-molybdate). However, microalbumin assays are not affected and can be used to monitor urinary protein excretion during VIBATIV treatment.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects: Pregnancy Category C

Pregnancy Exposure Registry

There is a pregnancy registry that monitors pregnancy outcomes in women exposed to VIBATIV during pregnancy. Physicians are encouraged to register pregnant patients, or pregnant women may enroll themselves in the VIBATIV pregnancy registry by calling 1-888-658-4228.

Fetal Risk Summary

All pregnancies have a background risk of birth defects (about 3%), pregnancy loss (about 15%), or other adverse outcomes regardless of drug exposure.

There are no data on VIBATIV use in pregnant women. In 3 animal species, VIBATIV exposure during pregnancy at clinically relevant doses caused reduced fetal weights and increased rates of digit and limb malformations in offspring. These data raise concern about potential adverse developmental outcomes in humans (see *Data*).

Clinical Considerations

Given the lack of human data and the risks suggested by animal data, avoid using VIBATIV in pregnant women unless the benefits to the patient outweigh the potential risks to the fetus.

Data

Human Data

There are no data on human pregnancies exposed to VIBATIV.

Animal Data

In embryo-fetal development studies in rats, rabbits, and minipigs, telavancin demonstrated the potential to cause limb and skeletal malformations when given intravenously during the

period of organogenesis at doses up to 150, 45 or 75 mg/kg/day, respectively. These doses resulted in exposure levels approximately 1- to 2-fold the human exposure (AUC) at the maximum clinical recommended dose. Malformations observed at <1% (but absent or at lower rates in historical or concurrent controls), included brachymelia (rats and rabbits), syndactyly (rats, minipigs), adactyly (rabbits), and polydactyly (minipigs). Additional findings in rabbits included flexed front paw and absent ulna, and in the minipigs included misshapen digits and deformed front leg. Fetal body weights were decreased in rats.

In a prenatal/perinatal development study, pregnant rats received intravenous telavancin at up to 150 mg/kg/day (approximately the same AUC as observed at the maximum clinical dose) from the start of organogenesis through lactation. Offspring showed decreases in fetal body weight and an increase in the number of stillborn pups. Brachymelia was also observed. Developmental milestones and fertility of the pups were unaffected.

8.3 Nursing Mothers

It is not known whether telavancin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when VIBATIV is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of VIBATIV in pediatric patients has not been studied.

8.5 Geriatric Use

Of the 929 patients treated with VIBATIV at a dose of 10 mg/kg once daily in clinical trials of cSSSI, 174 (18.7%) were ≥65 years of age and 87 (9.4%) were ≥75 years of age. In the cSSSI trials, lower clinical cure rates were observed in patients ≥65 years of age compared with those <65 years of age. Overall, treatment-emergent adverse events occurred with similar frequencies in patients ≥65 (75% of patients) and <65 years of age (83% of patients). Fifteen of 174 (8.6%) patients ≥65 years of age treated with telavancin had adverse events indicative of renal impairment compared to 16 of 755 (1.9%) patients <65 years of age *[see Warnings and Precautions (5.3), Clinical Trials (14.1)]*.

Telavancin is substantially excreted by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in this age group.

The mean plasma AUC values of telavancin were similar in healthy young and elderly subjects. Dosage adjustment for elderly patients should be based on renal function *[see Dosage and Administration, Clinical Pharmacology (12.3)]*.

8.6 Patients with Renal Impairment

The cSSSI trials included patients with normal renal function and patients with varying degrees of renal impairment. Patients with underlying renal dysfunction or risk factors for renal dysfunction had a higher incidence of renal adverse events *[see Warnings and Precautions (5.3)]*. Patients with creatinine clearance ≤50 mL/min also had lower clinical cure rates. Consider these data when selecting antibacterial therapy in patients with baseline moderate/ severe renal impairment (CrCl ≤50 mL/min).

Dosage adjustment is required in patients with ≤50 mL/min renal impairment *[see Dosage and Administration (2.2)]*. There is insufficient information to make specific dosage adjustment recommendations for patients with end-stage renal disease (CrCl <10 mL/min), including patients receiving hemodialysis *[see Overdosage (10), Clinical Pharmacology (12.3)]*.

Hydroxypropyl-beta-cyclodextrin is excreted in urine and may accumulate in patients with renal impairment. Serum creatinine should be closely monitored and, if renal toxicity is suspected, an alternative agent should be considered [*see Warnings and Precautions (5.3), Clinical Pharmacology (12.3)*].

8.7 Patients with Hepatic Impairment

The cSSSI trials included patients with normal hepatic function and with hepatic impairment. No dosage adjustment is recommended in patients with mild or moderate hepatic impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

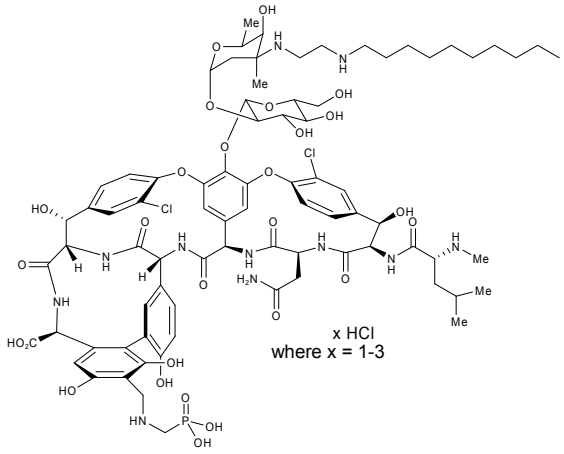
In the event of overdosage, VIBATIV should be discontinued and supportive care is advised with maintenance of glomerular filtration and careful monitoring of renal function. Following administration of a single dose of VIBATIV 7.5 mg/kg to subjects with end-stage renal disease, approximately 5.9% of the administered dose of telavancin was recovered in the dialysate following 4 hours of hemodialysis. However, no information is available on the use of hemodialysis to treat an overdosage *[see Clinical Pharmacology (12.3)]*.

The clearance of telavancin by continuous venovenous hemofiltration (CVVH) was evaluated in an in vitro study *[see Nonclinical Toxicology (13.2)]*. Telavancin was cleared by CVVH and the clearance of telavancin increased with increasing ultrafiltration rate. However, the clearance of telavancin by CVVH has not been evaluated in a clinical study; thus, the clinical significance of this finding and use of CVVH to treat an overdosage is unknown.

11 DESCRIPTION

VIBATIV contains telavancin hydrochloride, a lipoglycopeptide antibacterial that is a synthetic derivative of vancomycin. The chemical name of telavancin hydrochloride is vancomycin,N3''-[2-(decylamino)ethyl]-29-[[(phosphono-methyl)-amino]-methyl]-hydrochloride. Telavancin hydrochloride has the following chemical structure:

Figure 1: Telavancin Hydrochloride



Telavancin hydrochloride

Telavancin hydrochloride is an off-white to slightly colored amorphous powder with the empirical formula $C_{80}H_{106}C_{12}N_{11}O_{27}P$•xHCl (where x = 1 to 3) and a free-base molecular weight of 1755.6. It is highly lipophilic and slightly soluble in water.

VIBATIV is a sterile, preservative-free, white to slightly colored lyophilized powder containing telavancin hydrochloride (equivalent to either 250 mg or 750 mg of telavancin as the free base) for intravenous use. The inactive ingredients are Hydroxypropylbetadex, Ph. Eur (hydroxypropyl-beta-cyclodextrin) (2500 mg per 250 mg telavancin, 7500 mg per 750 mg telavancin), mannitol (312.5 mg per 250 mg telavancin, 937.5 mg per 750 mg telavancin),

and sodium hydroxide and hydrochloric acid used in minimal quantities for pH adjustment. When reconstituted, it forms a clear to slightly colored solution with a pH of 4.5 (4.0 to 5.0).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Telavancin is an antibacterial drug *[see Clinical Pharmacology (12.4)]*.

12.2 Pharmacodynamics

The antimicrobial activity of telavancin appears to best correlate with the ratio of area under the concentration-time curve to minimal inhibitory concentration (AUC/MIC) for S*taphylococcus aureus* based on animal models of infection. An exposure-response analysis of 2 cSSSI clinical trials supports the dose of 10 mg/kg every 24 hours.

Cardiac Electrophysiology

The effect of telavancin on cardiac repolarization was assessed in a randomized, double-blind, multiple-dose, positive-controlled, and placebo-controlled, parallel study (n=160). Healthy subjects received VIBATIV 7.5 mg/kg, VIBATIV 15 mg/kg, positive control, or placebo infused over 60 minutes once daily for 3 days. Based on interpolation of the data from VIBATIV 7.5 mg/kg and 15 mg/kg, the mean maximum baseline-corrected, placebo-corrected QTc prolongation at the end of infusion was estimated to be 12-15 msec for VIBATIV 10 mg/kg and 22 msec for the positive control (Table 5). By 1 hour after infusion the maximum QTc prolongation was 6-9 msec for VIBATIV and 15 msec for the positive control.

Table 5: Mean and Maximum QTcF Changes from Baseline Relative to Placebo

	QTcF[1] Change from Baseline	
	Mean (Upper 90% Confidence Limit[2]) msec	**Maximum (Upper 90% Confidence Limit) msec**
VIBATIV 7.5 mg/kg	4.1 (7)	11.6 (16)
VIBATIV 15 mg/kg	4.6 (8)	15.1 (20)
Positive Control	9.5 (13)	21.6 (26)

[1] Fridericia corrected

[2] Upper CL from a 2-sided 90% CI on difference from placebo (msec)

ECGs were performed prior to and during the treatment period in patients receiving VIBATIV 10 mg/kg in 3 studies to monitor QTc intervals. In these trials, 214 of 1029 (21%) patients allocated to treatment with VIBATIV and 164 of 1033 (16%) allocated to vancomycin received concomitant medications known to prolong the QTc interval and are known to be associated with definite or possible risk of torsades de pointes. The incidence of QTc prolongation >60 msec was 1.5% (15 patients) in the VIBATIV group and 0.6% (6 patients) in the vancomycin group. Nine of the 15 VIBATIV patients received concomitant medications known to prolong the QTc interval and definitely or possibly associated with a risk of torsades de pointes, compared with 1 of the 6 patients who received vancomycin. A similar number of patients in each treatment group (<1%) who did not receive a concomitant medication known to prolong the QTc interval experienced a prolongation >60 msec from baseline. In a separate analysis, 1 patient in the VIBATIV group and 2 patients in the vancomycin group experienced QTc >500 msec. No cardiac adverse events were ascribed to prolongation of the QTc interval.

12.3 Pharmacokinetics

The mean pharmacokinetic parameters of telavancin (10mg/kg) after a single and multiple 60-minute intravenous infusions (10 mg/kg every 24 hours) are summarized in Table 6.

Table 6: Pharmacokinetic Parameters of Telavancin in Healthy Adults, 10 mg/kg

	Single Dose	**Multiple Dose**
	(n=42)	**(n=36)**
C_{max} (mcg/mL)	93.6 ± 14.2	108 ± 26
$AUC_{0-\infty}$ (mcg·hr/mL)	747 ± 129	--[1]
AUC_{0-24h} (mcg·hr/mL)	666 ± 107	780 ± 125
$t_{1/2}$ (hr)	8.0 ± 1.5	8.1 ± 1.5
Cl (mL/hr/kg)	13.9 ± 2.9	13.1 ± 2.0
V_{ss} (mL/kg)	145 ± 23	133 ± 24

C_{max} maximum plasma concentration
AUC area under concentration-time course
$t_{1/2}$ terminal elimination half-life
Cl clearance
V_{ss} apparent volume of distribution at steady state
[1] Data not available

In healthy young adults, the pharmacokinetics of telavancin administered intravenously were linear following single doses from 5 to 12.5 mg/kg and multiple doses from 7.5 to 15 mg/kg

administered once-daily for up to 7 days. Steady-state concentrations were achieved by the third daily dose.

Distribution

Telavancin binds to human plasma proteins, primarily to serum albumin, in a concentration-independent manner. The mean binding is approximately 90% and is not affected by renal or hepatic impairment.

Concentrations of telavancin in skin blister fluid were 40% of those in plasma ($AUC_{0\text{-}24hr}$ ratio) after 3 daily doses of 7.5 mg/kg VIBATIV in healthy young adults.

Metabolism

No metabolites of telavancin were detected in in vitro studies using human liver microsomes, liver slices, hepatocytes, and kidney S9 fraction. None of the following recombinant CYP 450 isoforms were shown to metabolize telavancin in human liver microsomes: CYP 1A2, 2C9, 2C19, 2D6, 3A4, 3A5, 4A11. The clearance of telavancin is not expected to be altered by inhibitors of any of these enzymes.

In a mass balance study in male subjects using radiolabeled telavancin, 3 hydroxylated metabolites were identified with the predominant metabolite (THRX-651540) accounting for <10% of the radioactivity in urine and <2% of the radioactivity in plasma. The metabolic pathway for telavancin has not been identified.

Excretion

Telavancin is primarily eliminated by the kidney. In a mass balance study, approximately 76% of the administered dose was recovered from urine and <1% of the dose was recovered from feces (collected up to 216 hours) based on total radioactivity.

Specific Populations

Geriatric Patients

The impact of age on the pharmacokinetics of telavancin was evaluated in healthy young (range 21-42 years) and elderly (range 65-83 years) subjects. The mean CrCl of elderly

subjects was 66 mL/min. Age alone did not have a clinically meaningful impact on the pharmacokinetics of telavancin *[see Use in Specific Populations (8.5)]*.

Pediatric Patients

The pharmacokinetics of telavancin in patients less than 18 years of age have not been studied.

Gender

The impact of gender on the pharmacokinetics of telavancin was evaluated in healthy male (n=8) and female (n=8) subjects. The pharmacokinetics of telavancin were similar in males and females. No dosage adjustment is recommended based on gender.

Renal Impairment

The pharmacokinetics of telavancin were evaluated in subjects with normal and subjects with varying degrees of renal impairment following administration of a single dose of telavancin 7.5 mg/kg (n=28). The mean $AUC_{0-\infty}$ values were approximately 13%, 29%, and 118% higher for subjects with CrCl >50 to 80 mL/min, CrCl 30 to 50 mL/min, and CrCl <30 mL/min, respectively, compared to subjects with normal renal function. Dosage adjustment is required in patients with CrCl ≤50 mL/min *[see Dosage and Administration (2.2)]*.

Creatinine clearance was estimated from serum creatinine based on the Cockcroft-Gault formula:

$$\text{CrCl} = \frac{[140 - \text{age (years)}] \times \text{ideal body weight (kg)}^*}{[72 \times \text{serum creatinine (mg/dL)}]} \{\times 0.85 \text{ for female patients}\}$$

*Use actual body weight if < ideal body weight (IBW)
IBW (male) = 50 kg + 0.9 kg/cm over 152 cm height
IBW (female) = 45.5 kg + 0.9 kg/cm over 152 cm height

Following administration of a single dose of VIBATIV 7.5 mg/kg to subjects with end-stage renal disease, approximately 5.9% of the administered dose of telavancin was recovered in the dialysate following 4 hours of hemodialysis. The effects of peritoneal dialysis have not been studied.

Following a single intravenous dose of VIBATIV 7.5 mg/kg, the clearance of hydroxypropyl-beta-cyclodextrin was reduced in subjects with renal impairment, resulting in a higher exposure to hydroxypropyl-beta-cyclodextrin. In subjects with mild, moderate, and severe renal impairment, the mean clearance values were 38%, 59%, and 82% lower, respectively, compared to subjects with normal renal function. Multiple infusions of VIBATIV may result in accumulation of hydroxypropyl-beta-cyclodextrin.

Hepatic Impairment

The pharmacokinetics of telavancin were not altered in subjects with moderate hepatic impairment (n= 8, Child-Pugh B) compared to healthy subjects with normal hepatic function matched for gender, age, and weight. The pharmacokinetics of telavancin have not been evaluated in patients with severe hepatic impairment (Child-Pugh C).

Drug Interactions

In Vitro

The inhibitory activity of telavancin against the following CYP 450 enzymes was evaluated in human liver microsomes: CYP 1A2, 2C9, 2C19, 2D6, and 3A4/5. Telavancin inhibited CYP 3A4/5 at potentially clinically relevant concentrations. Upon further evaluation in a Phase 1 clinical trial, telavancin was found not to inhibit the metabolism of midazolam, a sensitive CYP3A substrate (see below).

Midazolam

The impact of telavancin on the pharmacokinetics of midazolam (CYP 3A4/5 substrate) was evaluated in 16 healthy adult subjects following administration of a single dose of VIBATIV 10 mg/kg, intravenous midazolam 1 mg, and both. The results showed that telavancin had no impact on the pharmacokinetics of midazolam and midazolam had no effect on the pharmacokinetics of telavancin. Therefore, telavancin is unlikely to alter the pharmacokinetics of drugs metabolized by the CYP450 system to a clinically significant degree.

Aztreonam

The impact of telavancin on the pharmacokinetics of aztreonam was evaluated in 11 healthy adult subjects following administration of a single dose of VIBATIV 10 mg/kg, aztreonam

2 gm, and both. Telavancin had no impact on the pharmacokinetics of aztreonam and aztreonam had no effect on the pharmacokinetics of telavancin. No dosage adjustment of telavancin or aztreonam is recommended when both drugs are coadministered.

Piperacillin-tazobactam

The impact of telavancin on the pharmacokinetics of piperacillin-tazobactam was evaluated in 12 healthy adult subjects following administration of a single dose of VIBATIV 10 mg/kg, piperacillin-tazobactam 4.5 g, and both. Telavancin had no impact on the pharmacokinetics of piperacillin-tazobactam and piperacillin-tazobactam had no effect on the pharmacokinetics of telavancin. No dosage adjustment of telavancin or piperacillin-tazobactam is recommended when both drugs are coadministered.

12.4 Microbiology

Telavancin is a semisynthetic, lipoglycopeptide antibiotic. Telavancin exerts concentration-dependent, bactericidal activity against Gram-positive organisms in vitro, as demonstrated by time-kill assays and MBC/MIC (minimum bactericidal concentration/minimum inhibitory concentration) ratios using broth dilution methodology. In vitro studies demonstrated a telavancin post-antibiotic effect ranging from 1 to 6 hours against *S. aureus* and other Gram-positive pathogens.

Although telavancin is approximately 90% protein bound, the presence of human serum or human serum albumin has minimal impact on the in vitro activity of telavancin against staphylococci, streptococci, and vancomycin-susceptible enterococci.

Mechanism of Action

Telavancin inhibits bacterial cell wall synthesis by interfering with the polymerization and cross-linking of peptidoglycan. Telavancin binds to the bacterial membrane and disrupts membrane barrier function.

Interactions with Other Antibacterials

In vitro investigations demonstrated no antagonism between telavancin and amikacin, aztreonam, cefepime, ceftriaxone, ciprofloxacin, gentamicin, imipenem, meropenem, oxacillin, piperacillin/tazobactam, rifampin, and trimethoprim/sulfamethoxazole, when tested

in various combinations against telavancin susceptible staphylococci, streptococci, and enterococci. This information is not available for other bacteria.

Cross-Resistance

Some vancomycin-resistant enterococci have a reduced susceptibility to telavancin. There is no known cross-resistance between telavancin and other classes of antibiotics.

Antibacterial Activity

Telavancin has been shown to be active against most isolates of the following microorganisms both in vitro and in clinical infections as described in the Indications and Usage section *[see Indications and Usage (1.1)]*:

Facultative Gram-Positive Microorganisms

Staphylococcus aureus (including methicillin-resistant isolates)
Streptococcus pyogenes
Enterococcus faecalis (vancomycin-susceptible isolates only)
Streptococcus agalactiae
Streptococcus anginosus group (includes *S. anginosus, S. intermedius,* and *S. constellatus*)

Greater than 90% of the following microorganisms exhibit an in vitro MIC less than or equal to the telavancin-susceptible breakpoint for organisms of similar genus shown in Table 7. The safety and effectiveness of telavancin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Facultative Gram-Positive Microorganisms

Enterococcus faecium (vancomycin-susceptible isolates only)
Staphylococcus haemolyticus
Streptococcus dysgalactaie subsp. *equisimilis*
Staphylococcus epidermidis

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide cumulative results of the in vitro susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution technique

Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure *[see References (15)]*. Standardized procedures are based on a dilution method (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of telavancin powder. The MIC values should be interpreted according to the criteria provided in Table 7.

Diffusion technique

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure requires the use of standardized inoculum concentrations *[see References (15)]*. This procedure uses paper disks impregnated with 30 mcg of telavancin to test the susceptibility of microorganisms to telavancin. The disk diffusion interpretive criteria are provided in Table 7.

Table 7: Susceptibility Interpretive Criteria for Telavancin

	Susceptibility Interpretive Criteria[1]					
	Minimal inhibitory concentration (mcg/mL)			**Disk Diffusion zone diameter (mm)**		
	S	**I**	**R**	**S**	**I**	**R**
Staphylococcus aureus (including methicillin-resistant isolates)	≤ 1	--	--	≥ 15	--	--
Streptococcus pyogenes *Streptococcus agalactiae* *Streptococcus anginosus group*	≤ 0.12	--	--	≥ 15	--	--
Enterococcus faecalis (vancomycin-susceptible isolates only)	≤ 1	--	--	≥ 15	--	--

1 The current absence of resistant isolates precludes defining any results other than “susceptible” Isolates yielding results other than susceptible should be subjected to additional testing

A report of “susceptible" indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antimicrobial compound in the blood reaches the concentrations usually achievable.

Quality Control

Standardized susceptibility test procedures require the use of laboratory control microorganisms to monitor the performance of the supplies and reagents used in the assay, and the techniques of the individuals performing the test. Standard telavancin powder should provide the range of values noted in Table 8.

Quality control microorganisms are specific strains of organisms with intrinsic biological properties relating to resistance mechanisms and their genetic expression within bacteria; the specific strains used for microbiological quality control are not clinically significant.

Table 8: Acceptable Quality Control Ranges for Telavancin to be used in Validation of Susceptibility Test Results

	Acceptable Quality Control Ranges	
	Minimal Inhibitory Concentration (mcg/mL)	**Disk Diffusion Zone Diameter (mm)**
Enterococcus faecalis ATCC 29212	0.12-0.5	Not applicable
Staphylococcus aureus ATCC 29213	0.12-1	Not applicable
Staphylococcus aureus ATCC 25923	Not applicable	16-20
Streptococcus pneumoniae ATCC 49619[1]	0.004-0.03	17-24

[1] This organism may be used for validation of susceptibility test results when testing *Streptococcus* spp. other than *S. pneumoniae*

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to determine the carcinogenic potential of telavancin have not been performed.

Neither mutagenic nor clastogenic potential of telavancin was found in a battery of tests including: assays for mutagenicity (Ames bacterial reversion), an in vitro chromosome aberration assay in human lymphocytes, and an in vivo mouse micronucleus assay.

Telavancin did not affect the fertility or reproductive performance of adult male rats (exposed to telavancin for at least 4 weeks prior to mating) or female rats (exposed to telavancin for at least 2 weeks prior to mating).

Male rats given telavancin for 6 weeks, at exposures similar to those measured in clinical studies, displayed altered sperm parameters that were reversible following an 8-week recovery period.

13.2 Animal Toxicology and/or Pharmacology

Two-week administration of telavancin in rats produced minimal renal tubular vacuolization with no changes in BUN or creatinine. These effects were not seen in studies conducted in dogs for similar duration. Four weeks of treatment resulted in reversible elevations in BUN and/or creatinine in association with renal tubular degeneration that further progressed following 13 weeks of treatment.

These effects occurred at exposures (based on AUCs) that were similar to those measured in clinical trials.

The potential effects of continuous venovenous hemofiltration (CVVH) on the clearance of telavancin were examined in an in vitro model using bovine blood. Telavancin was cleared by CVVH and the clearance of telavancin increased with increasing ultrafiltration rate *[see Overdosage (10)*].

14 CLINICAL TRIALS

14.1 Complicated Skin and Skin Structure Infections

Adult patients with clinically documented complicated skin and skin structure infections (cSSSI) were enrolled in two randomized, multinational, multicenter, double-blinded trials (Trial 1 and Trial 2) comparing VIBATIV (10 mg/kg IV every 24 hours) with vancomycin (1 g IV every 12 hours) for 7 to 14 days. Vancomycin dosages could be adjusted per site-specific practice. Patients could receive concomitant aztreonam or metronidazole for suspected Gram-negative and anaerobic infection, respectively. These trials were identical in design, enrolling approximately 69% of their patients from the United States.

The trials enrolled adult patients with cSSSI with suspected or confirmed MRSA as the primary cause of infection. The all-treated efficacy (ATe) population included all patients who received any amount of study medication according to their randomized treatment group and were evaluated for efficacy. The clinically evaluable population (CE) included patients in the ATe population with sufficient adherence to the protocol.

The ATe population consisted of 1,794 patients. Of these, 1,410 (78.6%) patients were clinically evaluable (CE). Patients with demographic and baseline characteristics were well-balanced between treatment groups and are presented in Table 9.

Table 9: Baseline Infection Types in Patients in Trials 1 and 2 – ATe Population

	VIBATIV (N=884)[1]	**Vancomycin (N=910)[1]**
Type of infection		
Major Abscess	375 (42.4%)	397 (43.6%)
Deep/Extensive Cellulitis	309 (35.0%)	337 (37.0%)
Wound Infection	139 (15.7%)	121 (13.3%)
Infected Ulcer	45 (5.1%)	46 (5.1%)
Infected Burn	16 (1.8%)	9 (1.0%)

[1] Includes all patients randomized, treated, and evaluated for efficacy

The primary efficacy endpoints in both trials was the clinical cure rates at a follow-up (Test of Cure) visit in the ATe and CE populations. Clinical cure rates in Trials 1 and 2 are displayed for the ATe and CE population in Table 10.

Table 10: Clinical Cure at Test-of-Cure in Trials 1 and 2 - ATe and CE Populations

	Trial 1			**Trial 2**		
	VIBATIV	**Vancomycin**	**Difference**	**VIBATIV**	**Vancomycin**	**Difference**
	% (n/N)	**% (n/N)**	**(95% CI)[1]**	**% (n/N)**	**% (n/N)**	**(95% CI)[1]**
ATe	72.5%	71.6%	0.9	74.7%	74.0%	0.7
	(309/426)	(307/429)	(-5.3, 7.2)	(342/458)	(356/481)	(-5.1, 6.5)
CE	84.3%	82.8%	1.5	83.9%	87.7%	-3.8
	(289/343)	(288/348)	(-4.3, 7.3)	(302/360)	(315/359)	(-9.2, 1.5)

[1]95% CI computed using a continuity correction

The cure rates by pathogen for the microbiologically evaluable (ME) population are presented in Table 11.

Table 11: Clinical Cure Rates at the Test-of-Cure for the Most Common Pathogens in Trials 1 and 2 – ME Population[1]

	VIBATIV % (n/N)	**Vancomycin % (n/N)**
Staphylococcus aureus (MRSA)	87.0% (208/239)	85.9% (225/262)

	VIBATIV % (n/N)	Vancomycin % (n/N)
Staphylococcus aureus (MSSA)	82.0% (132/161)	85.1% (131/154)
Enterococcus faecalis	95.6% (22/23)	80.0% (28/35)
Streptococcus pyogenes	84.2% (16/19)	90.5% (19/21)
Streptococcus agalactiae	73.7% (14/19)	86.7% (13/15)
Streptococcus anginosus group	76.5% (13/17)	100.0% (9/9)

[1] The ME population included patients in the CE population who had Gram positive pathogens isolated at baseline and had central identification and susceptibility of the microbiological isolate(s)

In the two cSSSI trials, clinical cure rates were similar across gender and race. Clinical cure rates in the telavancin clinically evaluable (CE) population were lower in patients ≥65 years of age compared to those <65 years of age. A decrease of this magnitude was not observed in the vancomycin CE population. Clinical cure rates in the telavancin CE population <65 years of age were 503/581 (86.6%) and in those ≥65 years were 88/122 (72.1%). In the vancomycin CE population clinical cure rates in patients <65 years of age were 492/570 (86.3%) and in those ≥65 years was 111/137 (82.0%). Clinical cure rates in the telavancin-treated patients were lower in patients with baseline CrCl ≤50 mL/min compared to those with CrCl >50 mL/min. A decrease of this magnitude was not observed in the vancomycin-treated patients *[see Warnings and Precautions (5.4)]*.

15 REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI). Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard – 8th ed., CLSI document M7-A8, CLSI, 940 West Valley Rd., Suite 1400, Wayne, PA. 19087-1898, 2009.

2. CLSI. Performance Standards for Antimicrobial Disk Susceptibility Tests, Approved Standard – 10th ed. CLSI document M2-A10; CLSI, Wayne, PA. 19087-1898, 2009.

3. CLSI. Performance Standards for Antimicrobial Susceptibility Testing - 19th Informational Supplement. CLSI document M100-S19, CLSI, Wayne, PA. 19087-1898, 2009.

16 HOW SUPPLIED/STORAGE AND HANDLING

- Cartons of 10 individually packaged 250 mg single-dose vials (NDC 0469-3525-30)
- Cartons of 10 individually packaged 750 mg single-dose vials (NDC 0469-3575-50)

Store original packages at refrigerated temperatures of 2 to 8°C (35 to 46 °F). Excursions to ambient temperatures (up to 25 °C (77 °F)) are acceptable. Avoid excessive heat.

17 PATIENT COUNSELING INFORMATION

See Medication Guide.

Use during Pregnancy and by Women of Childbearing Potential

Women of childbearing potential (those who have **not** had: complete absence of menses for at least 24 months or medically confirmed menopause, medically confirmed primary ovarian failure, a history of hysterectomy, bilateral oophorectomy, or tubal ligation) should:

- Be informed about the potential risk of fetal harm if VIBATIV is used during pregnancy
- Have a pregnancy test prior to administration of VIBATIV
- If not pregnant, use effective contraceptive methods to prevent pregnancy during VIBATIV treatment
- Notify their prescribing physician/ healthcare provider if they become pregnant during VIBATIV treatment

Pregnancy Registry

There is a pregnancy registry that monitors pregnancy outcomes in women exposed to VIBATIV during pregnancy. Physicians are encouraged to register pregnant patients, or pregnant women may enroll themselves in the pregnancy registry by calling 1-888-658-4228.

Diarrhea

Diarrhea is a common problem caused by antibiotics that usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as 2 or

more months after having received the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Correct Use of Antibacterial Drugs

Patients should be counseled that antibacterial drugs including VIBATIV should only be used to treat bacterial infections. They do not treat viral infections (eg, the common cold). When VIBATIV is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may: (1) decrease the effectiveness of immediate treatment, and (2) increase the likelihood that the bacteria will develop resistance and will not be treatable by VIBATIV or other antibacterial drugs in the future.

Common Adverse Effects

Patients should be informed about the common adverse effects of VIBATIV including taste disturbance, nausea, vomiting, headache, and foamy urine. Patients should be instructed to inform their healthcare provider if they develop any unusual symptom, or if any known symptom persists or worsens. Patients should be instructed to inform their healthcare provider of any other medications they are currently taking with VIBATIV, including over-the-counter medications.

Manufactured and Marketed by:

Theravance, Inc.
South San Francisco, CA 94080

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